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HEBERDEN ORATION*

THE PROTEINS OF CONNECTIVE TISSUE AND THEIR METABOLISM

BY

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It is a great honour you have conferred upon me in asking me to deliver the Heberden Oration for 1959. By inviting a scientist whose main contributions have not been in the field of clinical medicine you have expressed a belief, which I share, that important advances in our knowledge of the diseases of connective tissue are likely to come from biochemistry, immunology, and biophysics, and in saying this I do not want to minimize the continuing importance of carefully controlled clinical observations.

The man we are honouring today, William Heberden, was a great gentleman and a scholar who was proficient in Latin, Greek, and Hebrew, but above all he was a great clinician. Heberden was, I believe, the first person to separate clearly smallpox from chickenpox; he was also the first to describe night blindness, but probably his most important contribution was to give a complete clinical picture of angina pectoris which was done in 1768. The underlying pathology of this disease, of which John Hunter was a sufferer, was not understood by Heberden, but was elucidated a little later by Heberden's friend, Edward Jenner, who was the first to describe the characteristic changes in the coronary vessels. The discovery of the subcutaneous nodules which are found in a large proportion of cases of rheumatic disease and which are named after Heberden, is probably one of his relatively minor contributions. But William Heberden was not only a very good clinical observer; he was interested in natural science in general. Apart from being a Fellow of the Royal College of Physicians, he was elected a Fellow of the Royal Society at the age of 39, admittedly at a time in our history when the proportion of medical men in the Royal Society was much greater than it is now. Heberden published several papers in the *Philosophical Transactions* on medical and meteorological subjects and his critical writings and lectures on materia medica had probably considerable influence on the reform of the Pharmacopoeia in 1788, which finally purged the latter of superstitious polypharmacy. We cannot nowadays aspire to attain the breadth of interest and achievement which characterized the life of William Heberden, but we may express the hope that a broad educational background and a lack of professional narrowness will remain distinguishing marks of British medicine in the future as they have been in the past.

The subject of this lecture is concerned with the proteins of connective tissue of which quantitatively the most important is collagen. This protein or group of proteins is widely distributed over all phyla of the animal kingdom, the one exception being the protozoa in which, to my knowledge, nobody has yet succeeded to demonstrate the presence of collagen. These somewhat unusual proteins which have almost entirely mechanical functions in nature are distinguished by several properties. One of the most characteristic features of this group of proteins is the large-angle *x*-ray diffraction pattern to which Astbury first drew attention. In particular he emphasized the 2·86 Å meridional reflexion which he thought represented the length of the peptide chain along the fibre axis and to the equatorial reflexions of 10 to 15 Å, which were attributed to the separation of the main chains. In addition, collagens also have a characteristic small-angle *x*-ray pattern of about 640 Å, which was at first interpreted as indicating the length of the molecule.

* Delivered by Professor A. Neuberger, F.R.S., December 4, 1959, at the Wellcome Foundation, London, W.C.1.

The 600 to 640 Å pattern is also observed in electron micrographs of teased collagen fibrils and this represents a unique feature of collagen of special diagnostic importance. It has been known for some time, through the work of Nageotte (1927), Fauré-Fremiet (1933), and Wyckoff and Corey (1936), that part of the collagen of rat tendon and of the fish swim bladder is soluble in dilute buffer solutions of low pH. By adjustment of pH and ionic strength and/or by addition of ionized organic substances of high negative valency, the collagen can be precipitated in the form of fibres. These fibres may, depending on the conditions of precipitation, have a structure resembling the native pattern, *i.e.* a periodicity of about 600-700 Å, one of approximately 200 Å, they may manifest an identity period of 2,600-3,000 Å, or finally they may be featureless electron-microscopically, *i.e.* show no band structure at all. These findings have been fully discussed by Schmitt (1959).

To the biochemist the most characteristic feature of collagen is its most unusual amino acid composition. Collagen contains no tryptophan and no cystine, and only small amounts of tyrosine, histidine, and methionine. On the other hand, it is rich in glycine, and in all the collagens of vertebrates and invertebrates alike so far investigated, glycine forms approximately one-third of all amino acids present. Collagens contain fairly large, but variable, amounts of proline and two amino acids, hydroxyproline and hydroxylysine, which have not been found in any other animal protein, apart from elastin which yields a small amount of hydroxyproline (Table I).

TABLE I

AMINO ACID ANALYSIS OF DIFFERENT COLLAGENS
(No. of residues per 1,000 total residues)

Amino Acids	Collagens		
	Steer Skin Gelatin	*Coelenterata* Skin	Spongin A
Glycine	334·0	311·0	315·0
Proline	131·0	63·0	78·0
Hydroxyproline	91·0	49·0	108·0
Tyrosine	4·7	7·9	4·7
Hydroxylysine	6·8	25·0	12·0
Lysine	25·0	27·0	9·0
Histidine	4·6	5·1	3·9

The great variability of the proline and hydroxyproline values in collagens from invertebrates have been emphasized by Watson (1958) and by Piez and Gross (1959), and the smaller but definite differences in amino acid composition of vertebrate collagens have been discussed by Eastoe and Leach (1958). Mammalian collagens appear to show smaller variations between species and many of these are probably not outside the limits of error of the method used. However, there is good evidence that collagens from different mammalian species are different (Table II).

TABLE II

AMINO ACID COMPOSITION OF COLLAGENS OF VERTEBRATES
(No. of residues per 1,000 total residues)

Amino Acids	Vertebrate Collagens				
	Ox Skin	Ox Tendon	Human Bone	Chicken Tendon	Lungfish Skin
Glycine	338·0	327·0	319·0	330·0	327·0
Proline	122·0	114·7	123·0	129·1	129·0
Histidine	4·5	4·8	5·8	4·2	4·5
Hydroxyproline	99·6	101·5	100·2	97·3	78·2
Hydroxylysine	6·3	—	3·5	9·6	6·3
Lysine	28·6	33·2	28·0	19·0	23·5

This can be deduced with a high degree of probability from the careful amino acid analyses of Eastoe and Leach (1958), but in addition Watson, Rothbard, and Vanamee (1954) found that the complement fixation which can be produced in rabbits after injection of soluble collagen is specific with regard to species, but apparently not with respect to the tissue from which the collagen had been obtained. On the other hand, Pietz and Likins (1957) found relatively large differences in the hydroxylysine contents of collagens isolated from tissues such as bone, tendon, tail, and dentin of the rat (Table III).

TABLE III

CONCENTRATIONS OF LYSINE AND HYDROXYLYSINE IN SEVERAL COLLAGENS OF THE RAT
(N as percentage of total N)
(Data from Piez and Likins, 1957)

Rat Collagen	Hydroxylysine	Lysine	Lysine : Hydroxylysine
Skin	0·81	4·68	5·8
Tail	1·05	3·78	3·6
Bone	1·74	3·6	1·93
Dentin	2·29	2·58	1·11

These findings, together with amino acid analyses of Eastoe and others, make it almost certain that the collagens derived from different tissues of the same mammal are not identical.

In this connexion we must briefly consider reticulin, the nature of which was discussed recently by Robb-Smith (1958). Reticulin fibres differ from collagen fibres in several respects, and their most characteristic property is that they appear black on applying the silver impregnation method of Bielschowsky. Moreover, reticulin is not readily

transformed into gelatin. There is no doubt that the main protein of the reticulin fibre has an amino acid composition which differs little from that of other mammalian collagens. The analyses of Windrum, Kent, and Eastoe (1955) show that human reticulum of kidney has somewhat higher hydroxyproline and hydroxylysine contents than collagens obtained from other human tissues. The reticulum fibre, in contrast to the collagen fibre, contains carbohydrate and fatty acids, mainly myristic acid. The arguments and the confusion which have arisen over this question is to a large extent due to the fact that the word "reticulin" has been applied both to the whole material comprising the microscopically visible fibre and to the protein which is in fact only a special type of collagen, forming the main constituent of the fibre.

Fibrous collagen is found exclusively outside cells, and its concentration in a particular tissue is inversely related to cell number and directly related to the sodium content of a tissue. Thus, about 90 per cent. of the dry weight of the almost completely acellular tendon of the adult is composed of collagen, and in this particular type of tissue the concentration of sodium is greatly in excess of that of potassium. A similar situation exists in the skin, where the collagen content varies more widely, but here too the sodium ion is present in relatively high concentration. In bone, too, collagen again is the predominant organic constituent, the amount of other proteins being exceedingly small, but here the correlation with sodium content is complicated by the large preponderance of apatite crystals which are present as solid phase and which apparently contain sodium ions in the crystal lattice. Apart from lung and muscle, in which collagen is present in fairly large amounts, the various parts of the intestinal tract contain surprisingly large amounts of collagen, and in the stomach of the rat, collagen may form up to 24 per cent. of the total solids. In all these tissues collagen is present in morphologically well-defined fibres and is obviously extracellular. The reticulin fibres of the basement membrane of the kidney, spleen, and thyroid are closely associated with cells, but it is generally accepted that these structures are in fact extracellular. It would therefore seem that the collagen content of a tissue could serve as an indicator of the volume of extracellular space in tissues, and might be used as a check on values obtained by calculations based on sodium, chloride, or potassium content, or on similar calculations in which the volume of penetration of inulin and other substances, such as iodine-labelled serum albumin which penetrate only slowly or not at all into cells is used.

The generalization that all collagen is extracellular may not be strictly correct. Lenhoff, Kline, and Hurley (1957) have reported the presence of hydroxyproline in an apparently intracellular collagen-like protein of the stinging capsules of *Hydra*.

Before dealing with the metabolism of collagen, I may perhaps refer again to the molecular weight and structure. It has already been mentioned that, both by electron microscope and *x*-ray diffraction, a repeat pattern or periodicity of the fibre of about 600-700 Å was observed, and it was originally suggested that this gave a measure of the length of the molecule. However, the dimensions of the tropocollagen molecule, which is the monomeric unit of the polymer, were not determined until Boedtker and Doty (1955) showed that the soluble collagen from the swim bladder of the carp consists of highly asymmetrical rod-like molecules, with a diameter of 13·5 Å, an average length of 3,000 Å, and a molecular weight of approximately 345,000. Later, Doty and his colleagues (Doty and Nishihara, 1958) showed that soluble calf skin collagen has a similar molecular weight of 360,000, a length of 3,300 Å, and a diameter of 13·5 Å. On heating to temperatures between 15-40° C., depending on the origin of the collagen, denaturation occurs, which is associated with the splitting into particles of unequal molecular weight. It therefore seems that the fundamental units of collagen are amongst the most highly asymmetric structures found in nature, the ratio of length to width being well over 200. Fibrils of a width of a few hundred to a thousand Å can be observed in a dark-field microscope and are resolvable in an electron microscope, but the collagen fibres which are visible macroscopically or microscopically have diameters of microns rather than of Angström units and are formed both by a lengthwise and by a side-by-side association of actual collagen molecules. It is of interest that Hall (1956) has recently been able to make tropocollagen molecules visible directly in the electron microscope. Moreover, Hall and Doty (1958) have compared their values calculated from physico-chemical measurements with those obtained from direct observation with the electron microscope and have arrived at an average length for the molecule of 2,820 Å.

The Metabolism of Collagen

With the aid of stable isotopes, Schoenheimer showed more than 20 years ago, that a large part of the material of which the mammalian body is composed is metabolically not inert, but is apparently renewed at a rate, which seemed at the time

this work was done, remarkably fast. This renewal of body substance, particularly of protein, appeared to be independent of the renewal of cells, and was particularly high in organs such as liver where the mitotic rate is normally so low as to be negligible. It was then assumed that most or all proteins are metabolically unstable and that in fact this constant renewal is a characteristic property of all living matter. Our own early experiments (Neuberger, Perrone, and Slack, 1951) showed that the collagen obtained from the tail tendon of the rat was remarkably inert. Glycine labelled with ^{14}C was given in a single dose to adult rats and the animals were killed at suitable times after the injection, extending up to 7 weeks. The results showed that tendon collagen was completely or almost completely inert metabolically in the adult animal. The results indicated clearly that the half-life of the collagen of the tail tendon of the adult rat, if it turns over at all, is of the same order as the life-span of the animal itself. With rapidly growing rats, however, the position is different, and the incorporation of radioactive glycine into the collagen is rather high, and only slightly lower than the values found for the non-collagen proteins of liver and other proteins with relatively rapid turnover rates. But this radioactive collagen, once it is found, is fairly stable and persists for many months, during which time the labelled amino acids have almost completely disappeared from other proteins such as liver. The second point I want to mention is that tendon collagen is somewhat exceptional in its metabolic inertia. In the experiments just mentioned, we also examined the behaviour of collagens from bone, skin, and liver. The collagens in these tissues, even in adult animals, are not completely inert, and the collagens of bone and liver turn over at rates which are quite appreciable, but still extremely low when compared with those of non-collagen proteins of liver. That collagen in certain tissues can be built up and broken down fairly readily under certain well-defined physiological conditions can be seen from the work of Harkness and Harkness (1954), who have demonstrated very striking changes in the collagen content of the uterus of the rat during pregnancy and lactation. A more recent demonstration of this metabolic lability of collagen is provided by the experiments of Harkness, Harkness, and James (1958). These authors fed a protein-free diet to adult mice and examined the changes in the collagen content of the whole body. The protein-free diet produced a loss of body weight of 40 per cent.; a loss of non-collagenous nitrogen of 35 per cent.; and a loss of collagen protein of 10 per cent. It was interesting that even under these fairly extreme conditions the loss of collagen was small, that the greater part of the loss was from the skin, and that only a relatively small part was lost from the viscera and the muscle. We may summarize these findings by stating that the various collagens of the body differ somewhat in their metabolic activity, going from the almost complete inertia of the tail tendon of the rat to the slow but significant turnover rates found with the collagens in other tissues such as skin or bone. In certain physiological conditions the rate of collagen turnover may be increased, and we are still completely ignorant as to the mechanisms which regulate these rates. We may assume that the enzymes which break down collagen are supplied by the cells of the connective tissue, possibly the fibroblasts, and the rate of collagen metabolism may be regulated by the cellularity of a tissue, which itself might be determined by hormonal and other factors.

Collagen and Bone Formation

It is generally accepted that there is a close functional relationship between the deposition of the mineral elements of bone and the metabolism of the organic matrix of bone, of which collagen comprises about 95 per cent. There are very few quantitative data on changes of collagen content of bone under various experimental conditions, but it appears (for references see Harkness and others, 1958) that a loss of calcium or phosphate, such as that produced through dietary deficiency, pregnancy, lactation, or administration or parathyroid extract, is generally associated with loss of organic matter, which is presumably mainly collagen. The loss of material from bone produced by immobilization and disuse appears to involve both organic and inorganic matter (Allison and Brooks, 1921). In clinical osteoporosis it is generally assumed that protein depletion is the primary cause, but here too the loss of collagen is followed by the radiologically observable reduction in mineral content. There is also strong evidence from observations made with physical and chemical techniques of an intimate association between inorganic elements and organic matrix. The interpretation of *x*-ray diffraction data of compact bone by Carlström and Engström (see Carlström, Engström, and Finean, 1955) has recently been questioned by others (*see* Clark and Iball, 1957; Glimcher, 1959), and the results obtained with the electron microscope are probably more conclusive. Several workers (Robinson and Watson, 1955; Fitton Jackson, 1957; Sheldon and Robinson, 1957) have recently shown that apatite crystals can actually occur within collagen fibres. It has also

been shown that a close association exists between the two types of crystalline structure, the collagen fibre and the apatite crystal, and that there is a parallel alignment between the inorganic crystal and the associated individual collagen fibre. It was also demonstrated by Solomons and Irving (1958) that the ϵ-amino groups of lysine and hydroxylysine residues in bone collagen cannot react with fluorodinitrobenzene until the tissue is decalcified, thus suggesting an intimate association between amino groups of collagen and apatite crystals. It is possible that a similar situation might exist for the guanidino groups of arginine.

The intimate morphological or even molecular association between collagen and apatite crystals found in bone explains the close metabolic interrelationship which manifests itself in physiological experiments and clinical experience. We may suggest that the collagen-apatite structure is normally fairly stable metabolically. However, when calcium is mobilized from bone through dietary or hormonal factors, the "naked" collagen fibre is now attacked by enzymes, as yet unidentified, and is degraded. Indeed it is not impossible that osteoclasts may carry and secrete such enzymes.

Collagen has also been considered responsible by many workers for the induction of crystallization by providing a catalytic surface for the nucleation of apatite crystals. It may be suggested that this activity is related to the electrochemical character of the protein. Mammalian collagens have isoionic points of about 9·1-9·3, and this is also indicated by amino acid analyses which suggest that there is a slight excess of basic groups in the protein. It appears likely that the bulk of the basic groups is separated from predominantly acidic parts of the molecules, and this is also indicated by the selective staining of certain bands of the fibre with phosphotungstic acid observable with the electron microscope. This "banding" has been interpreted as a specific interaction between the guanidino groups of arginine residues and the negatively-charged groups of the polyelectrolyte. The large shift of isoelectric point with increasing ionic strength of the solution, which was noted by Jackson and Neuberger (1957), and the observations of Veis, Anesey, and Cohen (1958) indicate that appreciable amounts of chloride, and presumably other anions, can be bound to collagen at a physiological pH and an ionic strength likely to be found in extracellular fluid. Indeed, the observations of Veis and others (1958) indicate that a pH of 7·4 and an ionic strength of 0·1, 0·16 mEq. NaCl or chloride ion is associated with 1 g. collagen. It would thus appear that collagen may bind *in vivo* also considerable amounts of chloride and possibly also of sodium, and that the collagen fibre acts like an ion-exchange resin, binding reversibly also substances such as mucopolysaccharides of the hyaluronic acid type. Such binding of chloride and possibly also of sodium may explain the unexpectedly high chloride sodium values reported by several workers for the tendon and skin of several species (Manery, 1954). It is thus suggested that a significant proportion of the chloride of the body is not in osmotic equilibrium with the inorganic salts of the plasma, but is bound to the collagen of the connective tissue.*

If we accept the idea now put forward that collagen binds chloride under physiological conditions, it follows that the basic regions of the fibre may also bind other ions such as phosphate, and this may be an important factor in the crystallization of bone salt. F. O. Schmitt and his colleagues, particularly A. J. Hodge, have recently carried out a number of experiments (for review *see* Glimcher, 1959) which strongly support the concept that collagen is involved in bone salt nucleation. It was found that collagen fibres showing the 640 Å axial repeat unit and reconstituted from soluble collagen of tendon, skin, bone, and other tissues are able to nucleate apatite crystals from supersaturated calcium phosphate solutions. Other types of fibres, such as paramyosin fibrils and collagen fibrils of 210 Å or 2,600 Å periodicity, did not induce crystallization. It would seem that the ability to induce nucleation does not reside in the steric arrangement of the collagen, *i.e.* the tropocollagen molecule, but in the arrangement of amino acid residues belonging to different tropocollagen molecules, but associated in the same fibril, and showing a favourable stereochemical relationship to one another. This important finding indicates that in the natural fibril form of collagen the macromolecules are polymerized both laterally and lengthwise in a specific fashion promoting the growth of calcium phosphate crystals.

These findings pose a number of new problems, one of which may be discussed here. It is not easy to see why calcification does not occur in tendon and skin normally, as these tissues are probably also, like plasma, supersaturated with respect to calcium and phosphate ions. In the first place it is possible that bone collagen may differ chemically from other collagens and may have a special activity of promoting nucleation. Secondly, the local concentrations of the free ions in the tissues may vary and may be determined by metabolic processes such

* Experiments recently carried out with insoluble tendon collagen have, however, not yielded conclusive evidence in favour of such binding of chloride as is postulated here.

as glycolysis, pH changes, and activity of enzymes. Indeed, the early suggestion of Robison that alkaline phosphate had a special role in bone formation may still have its place. But the most important factor regulating the concentration of free calcium ions is the type and concentration of mucopolysaccharides present in calcifying tissue. In this connexion two observations of the M.I.T. group are relevant. Several collagen-rich tissues, such as skin, failed to mineralize under conditions under which nucleation was observed with reconstituted fibres. However, crystallization was readily obtained after the tissues had been so treated that components of the ground substance, such as chondroitin sulphate, were removed, or after depolymerization of the chondroitin sulphate had been performed by the action of the appropriate enzyme. Moreover, hyaline cartilage, which is rich in acidic polysaccharides, removes calcium ions, but does not calcify. We may conclude that bone crystal formation depends on the special electrochemical properties of the tropocollagen molecule which facilitates specific binding of phosphate and possibly calcium ions, on the steric arrangement of collagen macromolecules in the fibril giving the best arrangement of amino acid side-chains for the formation of apatite nuclei, on the general metabolism of the tissue, and finally on the type and concentration of mucopolysaccharide present.

Fibrogenesis

It has been known for some time that varying proportions of the collagen of tissues can be extracted by treatment of the fibres with dilute organic acids or with acidic citrate buffers.

Orekhovitch, Tustanovsky, Orekhovitch, and Plotnikova (1948) and Orekhovitch and Shpikiter (1958) showed that the amount of this material decreased with the age of the animal, and they also obtained evidence by feeding ^{14}C-labelled glycine to animals that the total soluble collagen behaved as if it were a precursor of the insoluble collagen. Highberger, Gross, and Schmitt (1951) had shown in the meantime that there is in connective tissue, in addition to the collagen which is soluble in dilute acid, another fraction smaller in amount which is extracted by dilute salt solution at a neutral pH. The metabolic role of this "neutral salt-soluble collagen" (NSC) was investigated by my colleagues and myself (Harkness, Marko, Muir, and Neuberger, 1954) using isotopically labelled glycine in the rabbit. It was found that NSC behaved as might be expected for a collagen precursor: it became highly labelled within 18-36 hours after administration of the labelled glycine, but the radioactivity decreased rapidly after 2-3 days. The acid-soluble collagen also contained some labelled glycine, but the shape of the activity/time curve made exact interpretation difficult. These experiments were confirmed by D. S. Jackson (1957), who followed the changes in amounts and radioactivity of the various collagen fractions of a granuloma produced by injection of carrageenin, a technique introduced by Robertson and Schwartz (1953). My colleagues, Green and Lowther (1959), extended this work by carrying out their investigations *in vitro* and following the incorporation of [^{14}C]proline into the proline and hydroxyproline residues of the different collagen fractions (Table IV).

Table IV

Specific activities (c.p.m./μmol) of proline and hydroxyproline from collagen fractions, after 4 hrs incubation

Collagen Fractions	Hydroxyproline	Proline	Hydroproxyline : Proline
Neutral Salt-soluble Collagen ..	1,480·0	910·0	1·62
Acid-soluble Collagen ..	70·0	50·0	1·3
Insoluble Collagen ..	4·6 (3·8)	5·3 (3·9)	0·9 (1·0)

All three investigations led to the conclusion that the collagen fraction which is extractable by a buffer solution of neutral pH is newly-made protein. The question arises what are the physical or chemical differences between the various collagen fractions obtained from the same tissue. It is likely that such differences in amino acid composition as have been reported are not significant, and there is good evidence that neutral salt-soluble collagen and acid-soluble collagen are not markedly different in physical properties. It has been suggested that there exists in the connective tissue of growing animals a mixed population of collagen fibrils with a continuous gradation of solubility (Green and Lowther, 1959) and that the fraction extracted by salt at pH 7·0 represents poorly-integrated fibres (Gross, 1958). In other words, it is assumed that this fraction with a high turnover rate which represents collagen very recently synthesized has relatively few cross-linkages; as the fibre ages, its solubility decreases in a continuous fashion owing to the formation of an increasing number of cross-linkages, and this more stable three-dimensional organization is associated with a progressive loss of solubility.

The next question to be considered is the cytological location of the various collagen fibres. The

fraction which is extractable by acid is almost certainly present extracellularly in the form of fibres. This is the conclusion which must be drawn from the experiments of Jackson and Williams (1956) and also of Gross (1958), and other workers, who have found that the number of fine fibrils in a tissue section decreases after extraction with acidic buffers. But the possibility also exists that some of this fraction is derived from the outer layers of the coarser fibres. Part of the neutral salt-soluble fraction may also be derived from microscopically visible fibres or from very fine fibrils, but another part is almost certainly present inside the fibroblast, as can be deduced from unpublished experiments of my colleagues, Green and Lowther (1959). These workers incubated 10 g. of slices of granuloma containing mainly fibroblasts for 1 hr with [^{14}C] proline, essential amino acids, and glucose. The tissue was then sliced, crushed, and strained through a grid before homogenizing and differential centrifuging. The latter yielded a first fraction containing cell debris and coarser collagen fibres, a second fraction called the mitochondrial fraction which had been spun at 10,000 g. for 10 min., and a microsomal fraction which was obtained by centrifuging at 105,000 g. for 30 min. The mitochondrial fraction contained very few collagen fibres and also some microsomal material, as shown by electron microscopy (Figure).

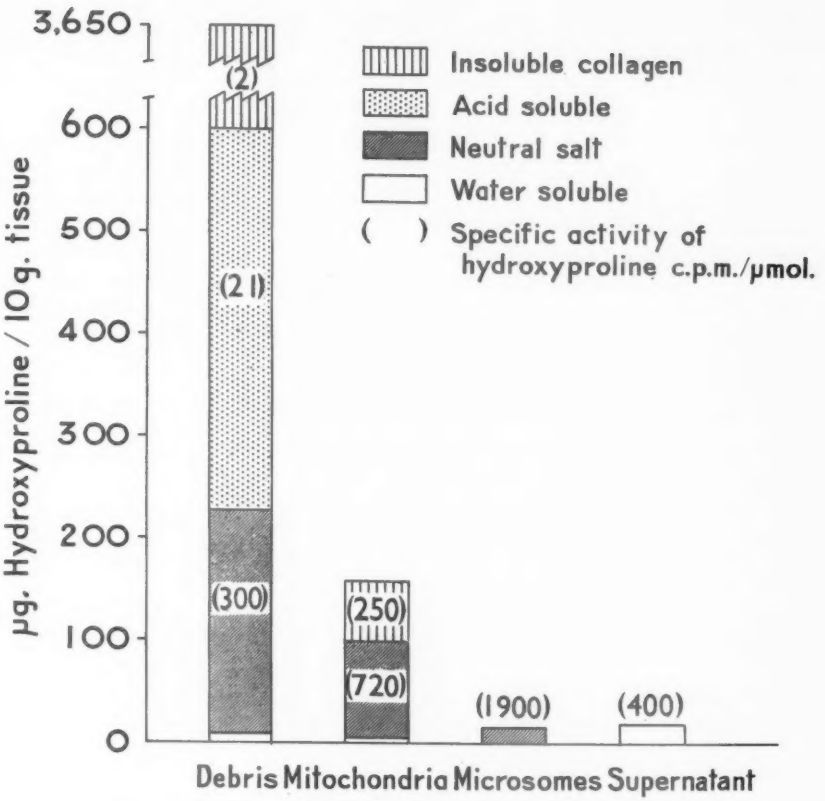

Figure.—Distribution of collagen between subcellular fractions of granuloma.

But the microsomal fraction contained practically no fibres visible under the electron microscope, was free of mitochondria and cell debris, and must be considered fairly homogenous. About 30-40 per cent. of the collagen present in the mitochondrial fraction was extracted by 0·14 M-NaCl, but there was also some insoluble collagen, presumably derived from fibres. The microsomal collagen could all be extracted with 0·14 M-NaCl. The specific radioactivity of the microsomal collagen was more than twice that of the mitochondrial collagen, and much higher than that of the collagen in the debris or supernatant fractions. The possibility that this highly active collagen is in fact derived from very fine extracellular fibrils very recently laid down cannot be completely excluded, but it seems to us unlikely, as the electron microscopic evidence indicates an almost complete absence of fibrils from the microsomal preparations. We believe that this fraction was in fact originally present in the microsomes of the fibroblast, and represents the earliest identifiable form of this protein. This conclusion is supported by experiments carried out in a parallel fashion to the St. Mary's work by Dr. J. A. Chapman of Professor Kellgren's department in Manchester. Dr. Chapman found that microsomal preparations contained spherical or ovoid vesicles, which were studded with particles, of diameters varying between 0·1 and 0·5µ in addition to more ill-defined material which resembles the endoplasmic reticulum found in other cells. The microsomal vesicles may be analogous to the vesicles observed in the pancreas (Siekevitz and Palade, 1958) or to the cytoplasmic ribonucleoprotein particles of rat liver described by Littlefield, Keller, Gross, and Zamecnik (1955), both of which show a high activity with respect to the incorporation

of amino acids into protein. There is admittedly a paucity of experimental facts, but, being conscious of the uncertain nature of our speculations, we may suggest that the microsomal structures observed in Chapman's electron micrographs are the site of collagen synthesis and are associated with the very soluble collagen fraction which gave the high radioactivity in the experiments of Green and Lowther.

It is now generally accepted that collagen fibres or fibrils, even those of a diameter of 150-400 Å are never found in cells, but that recently formed fibrils may be observed as being closely associated with the cell surface of the fibroblast (S. F. Jackson, 1957; Porter and Pappas, 1959). The latter workers come to the conclusion that unit fibrils of collagen organize within the cell surface and that further accretion to this unit fibril takes place through transport of soluble collagen from the interior of the fibroblast. Further growth of such fibrils to fibres observable under the light microscope is then likely to take place away from the cell surface in the ground substance.

The Importance of the Proteins of Connective Tissue in Disease

When Klemperer (1950) coined the term "collagen disease", he had the intention of collecting together a group of diseases which showed some common changes of the connective tissue upon microscopic study. At the time he believed that alteration of collagen fibres was a prime factor in this group of pathological conditions, but so far no positive findings to support this concept have been forthcoming. To the histologist the most significant phenomenon common to a variety of rheumatic and similar diseases is the fibrinoid degeneration of collagenous tissue. Fibrinoid nodules are by no means a unique characteristic of the so-called collagen diseases, and apart from the microscopically visible collagen fibres, the protein of these nodules contains very little hydroxyproline (Bien and Ziff, 1951). Consden, Glynn, and Stanier (1953) have reported similar findings, and from the amino acid composition of the material they have in fact concluded that the amount of fibrinogen or fibrinogen derivatives in these nodules must be small. On the other hand, Gitlin, Craig, and Janeway (1957), who have used a fluorescent antibody against fibrinogen, have obtained qualitative evidence that fibrinogen or material derived from fibrinogen is present in fibrinoid nodules. In any case, there is as yet, so far as I am aware, no clear-cut evidence to suggest that the presence of these nodules in the tissue is an indication of a specific disturbance in collagen metabolism.

Klemperer's concept has, in spite of the somewhat unfortunate nature of the term "collagen disease", had great value, drawing attention to the fact that the diseases thus grouped together present pathological changes which reside primarily in the connective tissue. His concept also stresses the fact that these diseases have many clinical features in common, and that these may have identical or similar aetiologies.

As I have implied, it is unlikely in my opinion that changes in collagen synthesis or breakdown are a prime factor in connective tissue disorders, and the question arises whether the biochemical study of other components of the ground substance, such as mucopolysaccharides, or of the systemic antibodies in this field of medicine may be more helpful to our understanding of the disease processes in connective tissue. It has been known for the last 10 years that at least half, but probably slightly more, of the total plasma proteins present in the body are outside the blood vessels, and suggestive evidence has become available, indicating that the classical concept of Starling, which implies that plasma proteins do not pass to any appreciable extent the epithelial lining of the capillaries, is not quite correct. Our own investigations (Humphrey, Neuberger, and Perkins, 1957) have shown that skin, in particular, contains significant quantities of serum proteins, and this may account for about 25 per cent. of that present in the extravascular space. The albumin was isolated by column electrophoresis and unambiguously identified by chemical, physical, and immunological methods, while the evidence for the presence of other plasma proteins was less complete. We have also obtained evidence for the presence of plasma proteins in tendon and loose connective tissue, and Gitlin, Nakasato, and Richardson (1955) have shown that the so-called myo-albumin of muscle is identical with serum albumin and is presumably present in the extracellular space of muscle. This more chemical evidence fully supports the results of the microscopic investigations carried out with the fluorescence antibody technique, such as those of Gitlin, Landing, and Whipple (1953), and there is thus no doubt that the larger part of, and possibly all, the plasma proteins present in the extravascular space is in fact located in the connective tissue.

If it is assumed, and I believe this is still only an assumption, that the connective tissue diseases are all caused by an antigen-antibody reaction and represent in fact the cellular response to such a reaction, the high concentration of plasma proteins

in the connective tissue is surely of importance. Connective tissue space in this connotation comprises not only skin, joints, tendon, etc., but also, for example, part of the arterial wall, the extracellular space of muscle, and the region round the basement membranes of the kidney. Connective tissue contains, apart from fibroblasts, histiocytes, macrophages, mast cells, plasma cells, and primitive mesenchymal cells; cells, which may, according to current opinion, be converted to one another, which are believed to be associated in varying degrees with antibody production, and which may also be concerned with the cellular response arising from antigen-antibody combination. We do not know whether the antigens active in rheumatic and other related diseases are extraneous to the body (*i.e.* whether they are *e.g.* components of the streptococcus), or whether they are derived from the cells of the patient himself, but it seems clear that connective tissue offers optimum conditions for closest contact between systemic antibodies and the various types of cells concerned with the antigen-antibody reaction. The localization of the disease process is thus readily explicable by the fact that both antigens, antibodies, cells concerned with antibody production, and cells participating in the physiological response to the antigen-antibody combination are present in connective tissue.

Finally, I should like to refer to the recent work of Watson and others (1954), which indicates that collagen of rat can induce the formation of specific antibodies in the rabbit. These antibodies are non-precipitating, but can be demonstrated by complement fixation. Very recently, this group of workers (Rothbard and Watson, 1959) has shown that specific lesions can be produced in rats if they are given an injection of an antiserum produced in rabbits by injections of rat collagen. The changes observed were confined to the kidney, and could only be produced under certain well-defined conditions, involving the preliminary immunization to normal rabbit globulins. It is difficult to assess the significance of these findings in relation to human disease, but the demonstration that an animal can be immunized to its own collagen has opened up a new line of approach.

I may perhaps finish this lecture by expressing the belief that a study of the non-collagen proteins of connective tissue, of the mucopolysaccharides and their metabolism, and particularly of the immunological reactions observed, may be more helpful to an understanding of connective tissue diseases than elucidation of collagen metabolism, important and interesting enough though this is to the biochemist and general biologist.

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THE LUBRICATION OF ANIMAL JOINTS IN RELATION TO SURGICAL RECONSTRUCTION BY ARTHROPLASTY*

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The accepted theory of joint lubrication is that of MacConaill (1932), who assembled arguments to show that it was an example of hydrodynamic or full-film lubrication.

The principal argument in applying the hydrodynamic theory to animal joints was the anatomical fact that in joints the curvatures of articulating surfaces are not completely congruous throughout their whole arc of movement. It was observed by Walmsley (1917, 1928) that the surfaces of the knee and hip are exactly congruous only in the position of full extension, which is the position of the motionless erect stance, but that in the arc employed for walking or running the convex surface has a slightly smaller radius than the concave surface. This presented to MacConaill's mind the existence of wedge-shaped spaces, occupied by wedge-shaped films of synovial fluid; it is the essence of the hydrodynamic theory that fluid pressure is generated in a wedge of lubricant as a result of the motion of the surfaces and that this pressure supports the load and keeps the sliding surfaces separated on a cushion of lubricant (Fig. 1).

Even before examining the problem experimentally in animal joints, there are theoretical criticisms which make the hydrodynamic theory unlikely. Firstly, the articular cartilage, which is present as a layer about $\frac{1}{8}$ in. thick over the sliding surfaces of the joint, is very resilient, being easily indented by pressure of the thumb-nail. An ankle-joint of an adult male has a projected surface area of less than 2 sq. in., so that a man weighing 12 st. carrying a 1-cwt. load on his shoulders will expose an ankle-joint to pressures of about 150 lb. per sq. in. There can be little doubt that these resilient surfaces are intimately applied to each other over the whole area especially when carrying loads.

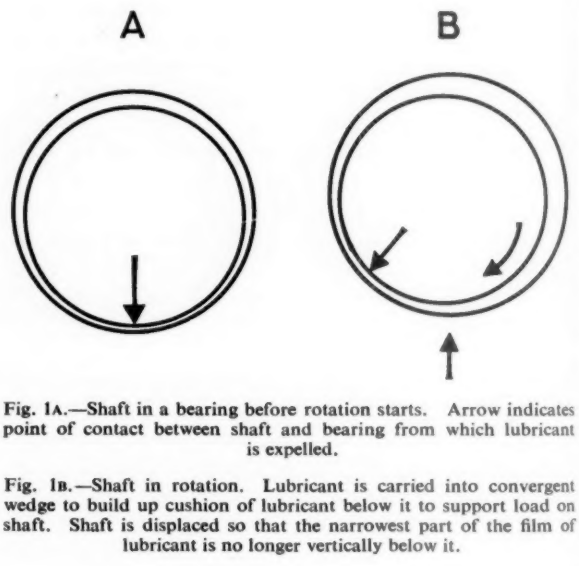

Fig. 1A.—Shaft in a bearing before rotation starts. Arrow indicates point of contact between shaft and bearing from which lubricant is expelled.

Fig. 1B.—Shaft in rotation. Lubricant is carried into convergent wedge to build up cushion of lubricant below it to support load on shaft. Shaft is displaced so that the narrowest part of the film of lubricant is no longer vertically below it.

Secondly, there is the well-known fact that hydrodynamic lubrication is not suited to conditions where the motion is reciprocating, because no sooner has a fluid wedge been established for motion in one direction than it is destroyed as motion starts in the other. Thirdly, hydrodynamic lubrication is not easy to achieve with slow-moving surfaces under heavy loads.

In hydrodynamic or full-film lubrication, the nature of the substances composing the sliding surfaces and the nature of the fluid used as a lubricant, are theoretically unimportant; the essentials are the geometry of the surfaces and the viscosity of the fluid. In this type of lubrication it is not necessary for the fluid to possess the property of "oiliness".

The form of lubrication which is the complete opposite of hydrodynamic lubrication is that known

* Based on a paper given at a joint meeting of the Heberden Society and the British Association of Physical Medicine on July 25, 1959.

as "boundary" lubrication (Bowden and Tabor, 1956). It is the antithesis of full-film lubrication in that the quality of the substances comprising the sliding surfaces and the quality of the fluid used as a lubricant are the essential features; the shape of the surfaces and viscosity of the fluid are unimportant. An example of the lack of correlation to viscosity is the fact that a watery solution of oleic acid is a better lubricant for glass sliding on glass than pure glycerine, though the latter is many times more viscous. In this type of lubrication the property of "oiliness" is fundamental, but, which is more important, it is not the "oiliness" of the lubricant itself but the property of oiliness when applied to the sliding surface. Thus methylated spirit has no more suggestion of oiliness than water when tested between the fingers, but for rubber it is a better lubricant than water. This illustrates the important fact that in boundary lubrication a lubricant has an affinity for the surface it lubricates, so that when motion takes place between two such lubricated surfaces it takes place between monomolecular films of lubricant chemically adherent to the underlying surface (Fig. 2). It is obvious that monomolecular films which are bound to the sliding surfaces are less likely to rupture under heavy loads than films of a lubricant which is inert towards the substance of the surface, because the integrity of such a film depends only on the intermolecular attraction in the fluid itself, and the intermolecular attraction of a fluid is obviously less than that of a solid. The molecules of a fluid which are bound to the surface of a solid lose the physical properties of a liquid. In the case of mineral oils, which have no chemical affinity for metals, the addition of small quantities of fatty acids greatly enhances their lubricating properties; this is explained by soaps being formed between the fatty acids and the metal, with the result that motion takes place between two layers of molecules all with their -COOH groups attached to the metal surface and the fatty chain projecting like the bristles of a brush.

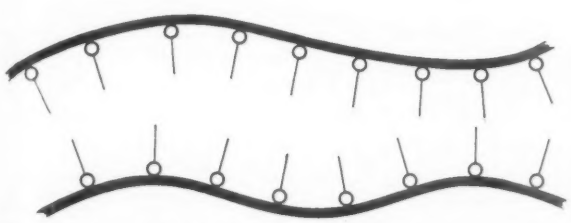

Fig. 2.—*Boundary Lubrication.* The irregular rubbing surfaces are separated by monomolecular films of lubricant bound to these surfaces by physico-chemical adhesion. The low-friction phenomenon is thus a function of low molecular attraction between the free ends of the adherent molecules of boundary lubricant.

This type of lubrication is exactly suited to the condition to which hydrodynamic (full-film) lubrication is not, that is, slow reciprocating motion under heavy loads. On these theoretical grounds it would seem that the conditions of joint lubrication are more akin to boundary lubrication than to full-film lubrication.

It is here that the greatest difficulty is encountered in lubrication theory, because in practice it is rare to find a pure example of either full-film or boundary lubrication and the commonest form of lubrication is a mixture of the two: "quasi-hydrodynamic" lubrication. Thus, in a bearing designed for true hydrodynamic lubrication, a full-film will be established only when the bearing is running at its calculated speed, while boundary conditions will be present when it is stationary. Similarly, in boundary lubrication, boundary conditions will exist only at the summits of elevated surface irregularities while in the intervening depressions hydrodynamic conditions are possible. With increasing speed the contribution of hydrodynamic lubrication will increase.

Coefficient of Friction of Articular Cartilage

The coefficient of friction, μ, is a simple ratio between the force necessary to make a body slide on a surface and the force pressing the body against the surface. A coefficient of friction of 0·1 means that a body will slide on a horizontal surface if a force equal to one-tenth of its weight is applied to it.

In the engineering laboratory it is easy to measure a coefficient of friction because one body can be made into a plane surface and the other body made to slide on it through the medium of a device for measuring force, such as a spring-balance. Unfortunately, articular cartilage cannot be fashioned into a plane surface and therefore estimation of its coefficient of friction offers special technical difficulties. The only record of this measurement to have been published is that of Jones (1934) who obtained the very low figure of 0·02. This figure was obtained by using a large joint from an ox, and although the design of the experiment showed great mechanical ingenuity, it was open to the theoretical objection that the ligaments of the joint were retained in their intact state in order to form an axis of motion to locate the rubbing surfaces on each other; the resistance to movement offered by these ligaments is an unknown quantity and theoretically might raise the recorded coefficient above its true value.

It was decided to attempt to make this measurement by sliding the femoral condyles of a freshly

amputated human knee-joint against the corresponding articular surface of the tibia after the ligaments and all extraneous tissues had been removed. To locate the rubbing surfaces against each other in the absence of ligaments, it was decided to use a ball-race, because this has a coefficient of friction which is constant for the conditions of the experiment and which may be estimated at about 0·001.

The mechanical difficulty is that the articular surfaces of the tibia are not flat and, under the influence of a load applied to the joint, there is a tendency for movement in one direction to be "uphill" and in the other direction "downhill". By restricting the movement between the rubbing surfaces to less than 3 mm., this difficulty was minimized. The tendency to spontaneous movement downhill under load was counteracted by using small balance weights to hold the slippery condyles in equilibrium on the downhill slope. The friction force was applied with the system in equilibrium and the mean was taken of the forces needed to slide the surface first uphill and then downhill.

APPARATUS.—The apparatus used in this experiment is illustrated diagrammatically in Fig. 3. The condyles of the femur A were attached rigidly to a horizontal beam B pivoted on roller bearings. Rocking of the beam on these bearings thus caused the articular surface of the condyles to move backward and forward on the arc of a circle of radius R. The arc was restricted to one or two degrees by suitable stops C. The roller bearings were located by two levers D, which permitted the femoral condyles to rise and fall; by this means the femoral surface could be lowered on to the tibial surface which was placed below it on a suitable platform. The load W ranging from 6 lb. to approximately 600 lb.,

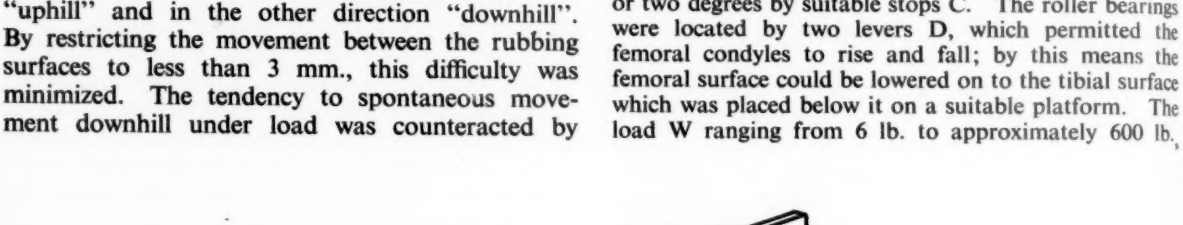

Fig. 3.—Arrangement to measure coefficient of friction in a cadaveric specimen of a human knee joint. (Courtesy of *Inst. mech. Eng.*, Proceedings of Symposium on Biomechanics, April 17, 1959, Fig. 22.)

(*a*) Arrangement

A	Condyles	D	Levers
B	Horizontal beam	E	Balance weights
C	Stops	W	Load

R Radius of circle

(*b*) Shape of rubbing surfaces indicated diagrammatically. The upper element is made to slide to and fro without rolling.

was applied to the rocking axis of the beam through Bowden cables by a system of levers. When the load was applied to the condyles the tendency for the beam to move spontaneously was counteracted, first by adjusting the position of the tibial surface under the femoral condyles, and secondly by applying small balance-weights E to one end of the beam to bring it into equilibrium. The position of equilibrium was adjusted between the stops C which restricted the arc of movement during the test. The force necessary to start the beam moving first in one direction and then in the other was then measured. To do this was easy when the joint was under heavy load; a spring-balance with a pointer which held a maximum reading was used to apply the force to move the beam first up and then down and to record the force at the moment when sliding started. When the joint was under light loading, the force needed to rock the beam was so low that a time factor became evident in relation to the rate at which the force was applied, which suggested a phenomenon of viscous flow. To make measurements in these circumstances a loop of chain was used with links of known weight, so that the force could be applied with a uniform rate of loading and repeated in opposite directions until a fair estimate could be made.

The coefficients obtained from seven experiments ranged from a minimum of 0·005 to a maximum of 0·023 (average 0·013).

In this series of experiments the most interesting feature was that no difference in the coefficient was observed when all visible traces of synovial fluid were removed by wiping the articular surfaces with a dry cloth or when the rubbing surfaces were freely lubricated with an excess of synovial fluid deliberately applied to the site of movement.

How extraordinarily low is this coefficient of friction 0·01 can be appreciated only if it is realized that it is approximately three times better than the coefficient for ice sliding on ice, which is approximately 0·03, and between ten and twenty times better than that for a polished steel surface moving on a lubricated brass bearing, which is within the range of 0·1 to 0·2.

The extraordinary fact of this very low coefficient of friction in an animal joint does not seem to have been observed by biologists. A coefficient of 0·01 means that a load of 100 lb. (the weight of a small adult) could be made to slide by applying a force of only 1 lb. If articular cartilage were to be no more slippery than a plain engine-bearing, the same load would need a force of 10-20 lb. to make it slide. If we consider that, in the lower extremity of a human being, four sliding surfaces are used simultaneously in each limb when walking or running (hip, knee, knee-cap, and ankle) we see that for an adult weighing 100 lb., 4 lb. would be needed to move all these joints, but, if lubricated metal bearings were substituted for the articular cartilage, a total force of 40-80 lb. would be needed to overcome frictional resistance. The remarkable way in which Nature has solved this friction problem will be appreciated when it is realized that to equal it an engineer would have to discard plain bearings and employ a so-called "frictionless" bearing where the rolling mechanism of a ball-race takes the place of sliding friction.

Pendulum Experiment

The most interesting experiment in the relatively small literature which exists on the mechanical aspects of joint lubrication is that described by Jones (1936), in which he used a pendulum method for measuring the coefficient of friction as described by Stanton (1923). By this method, a lubricated bearing is made the pivot of a pendulum. The coefficient of friction of the bearing can be calculated by comparing the rate of decay of amplitude as the pendulum swings on the test bearing with the rate of decay when the bearing is replaced by a frictionless knife-edge. This method presents a specially attractive feature, in that it is very easy to calculate the coefficient of friction at different speeds of sliding, the linear velocity at the rubbing surface being high when the amplitude is large and *vice versa*. It has been recognized since the early work of Coulomb (1866)* that within fairly wide limits the coefficient of friction is unaffected by the speed of sliding, and therefore that, if boundary conditions were to exist in the bearing at the pivot of the pendulum, the coefficient of friction should remain the same at all amplitudes of swing; if hydrodynamic conditions were to exist, the coefficient of friction should diminish with a diminishing amplitude of swing because the viscosity of fluids decreases with velocity.

To apply this theory to a joint, Jones used an intact finger joint amputated from the cadaver and by suitable means made it the pivot of a pendulum. He found that the coefficient of friction diminished as the amplitude of the swing diminished, and he therefore decided that the conditions of normal joint lubrication were hydrodynamic and not boundary. This experiment has been widely quoted in the literature to support the hydrodynamic theory, but two defects in the experiment present themselves:

(1) The surfaces of an interphalangeal joint are imperfectly congruous, and therefore to locate one surface on the other it is necessary to retain intact the ligaments of the joint. At large amplitudes the friction between the articular surfaces might appear

* See Bowden and Tabor (1956).

greater than the true value by work done in moving the ligaments and capsule; at low amplitudes the contribution of resistance from the capsule and ligaments would be less and the coefficient of friction would therefore appear lower at the small amplitudes.

(2) The lack of congruity in the joint would permit the articular surfaces to change from a true sliding motion at large amplitudes to a rolling motion at low amplitudes. At low amplitudes a rolling motion would present less resistance to movement than the sliding motion which would be superadded at large amplitudes.

Both these objections could explain a fall in the observed coefficient of friction with reduced amplitude of the pendulum without invoking viscosity and the theory of hydrodynamic lubrication.

To repeat this experiment it was necessary to find an animal joint possessing surfaces of a high degree of congruity in order to provide positive location for the rotation of one surface on the other in the absence of ligaments. The human ankle-joint is very suitable for this purpose because the cylindrical convexity of the upper surface of the talus is received into a deep concavity in the tibial surface and a stable location is maintained over quite large angles of movement.

A pendulum 45 in. in length carrying a bob weighing 30 lb. was attached to a cadaveric ankle-joint, as illustrated in Fig. 4. The talus was carried in the corresponding saddle-shaped articular surface of the tibia, which was mounted on a platform with an arrangement for tilting so that the actual bearing surface could be rendered horizontal. An arrangement was provided to elevate the pendulum and unload the surfaces under test in the interval between tests.

The amplitude of swing was measured cinematographically with a 16 frame/s. cine-camera photographing the movement of a pointer passing in front of a transparent illuminated scale. The maximum angular displacement of the bob from its position of rest was not more than 5° and the pendulum was set swinging by burning a string holding it at the starting position of deflection.

To find the rate of decay of amplitude due to air-damping, knife edges were substituted for the test specimen E.

The method of calculating the coefficient of friction has been reported in detail by Edwards (1959).

Two experiments of this type, using different specimens, were carried out, giving the following value for μ:

Experiment 2/11	$\mu = 0{\cdot}024$
Experiment 2/12	$\mu = 0{\cdot}014$

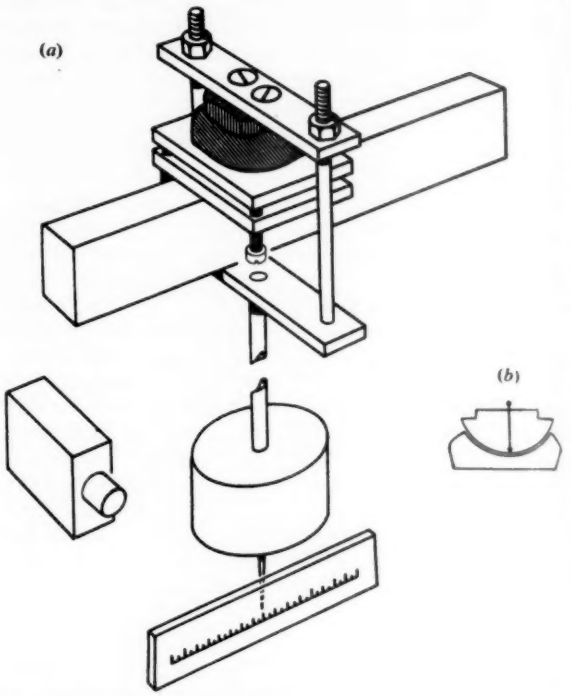

Fig. 4.—Stanton's pendulum arranged for the measurement of friction in a human ankle-joint. (Courtesy of *Inst. mech. Eng.*, Proceedings of Symposium on Biomechanics, April 17, 1959, Fig. 23.)

(*a*) Arrangement.

(*b*) Shape of rubbing surfaces indicated diagrammatically. In this arrangement the joint elements are upside down in relation to the erect position of the human body.

For comparison purposes, and for preliminary tests of the apparatus, the value of μ was obtained for metal surfaces lubricated with oil which had the same dimensions as the cylindrical surfaces of the human ankle-joint:

Experiment 2/3	
Brass/stainless steel/oil	$\mu = 0{\cdot}228$
Experiment 3/5	
Brass/P.T.F.E. (Polytetrafluorethylene)	$\mu = 0{\cdot}049$

These latter figures are consistent with reported values obtained by routine methods.

When plotted as a graph of amplitude against the number of the pendulum excursions (Fig. 5, opposite), it is seen that the decay of amplitude in the case of articular cartilage is linear, thus showing that the frictional resistance is the same at all speeds of sliding of the cartilage surfaces. This confirms the suspicion that the non-linear decrease in amplitude reported by Jones must have been due to the errors in design already suggested.

These experiments thus support the idea that the predominant mechanism in joint lubrication is a boundary phenomenon and that any quasi-hydrodynamic lubrication which theoretically might

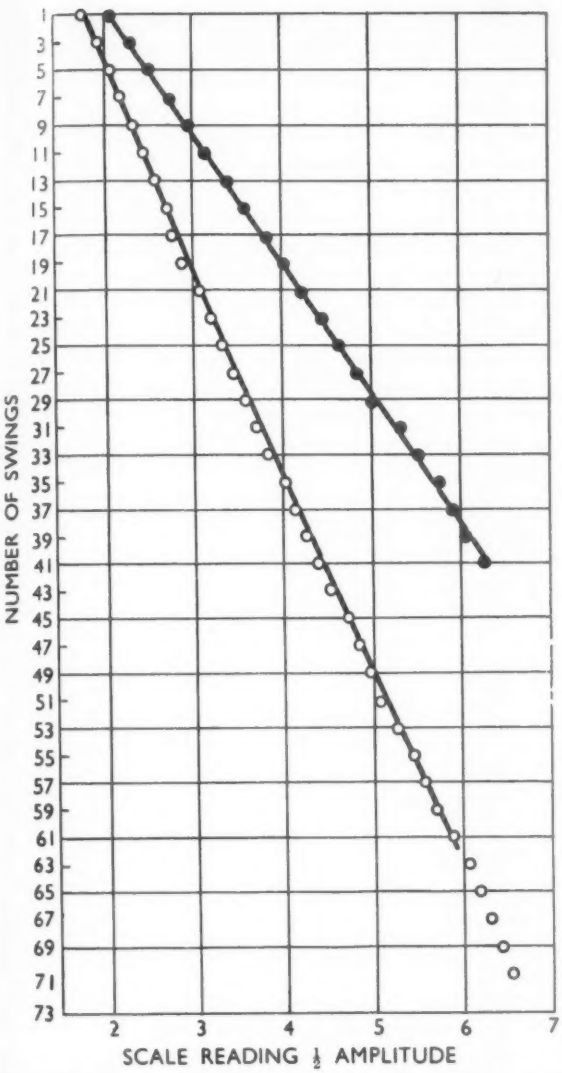

Fig. 5.—Decrease in swing plotted graphically showing, by the linear disposition of the parts, the constancy of the coefficient of friction with decreasing velocity of sliding, which is incompatible with the hydrodynamic theory of lubrication. (Courtesy of *Inst. mech. Eng.*, Proceedings of Symposium on Biomechanics, April 17, 1959, Fig. 24.)

● Experiment 11 ○ Experiment 12

develop as the speed rises is not present in the range of speeds covered by this experiment.

Synovial Fluid as a Lubricant

Another possibility which has to be considered as an explanation of the extraordinary low coefficient of friction in animal joints is that synovial fluid may possess properties as a lubricant unknown in engineering. Two pieces of experimental evidence suggesting this have been adduced by Ogston and Stanier (1953).

The first piece of evidence is that films of synovial fluid have a remarkable tenacity and resistance to rupture. By compressing a film of synovial fluid between a plane surface and a convex lens they were able to show from the measurement of Newton's rings that films of 20-50 mμ thickness would resist pressure of 10-100 kg./sq. cm. They attributed this behaviour to the molecular structure of the complex mucopolysaccharide, hyaluronic acid, which is responsible for the viscosity of synovial fluid: "the voluminous, randomly coiled particles may be thought of as being trapped and squeezed like a sponge, between the two surfaces".

The second piece of evidence is the finding that, as regards its viscosity, synovial fluid behaves in a non-Newtonian manner. To quote Ogston and Stanier: "The viscosity is very high at the lowest rates of shear, so that the joint is enabled to support a high load even at a low rate of movement. At higher rates of movement the viscosity falls, so that the drag of the joint is relatively lowered: the load which it will bear is not reduced, because the greater rate of movement more than offsets the fall in viscosity. A normal (Newtonian) fluid would not give these advantages."

It is evident that Ogston and Stanier are making the assumption that, at the higher rates of shear, the joint is lubricated by a fluid of low viscosity under hydrodynamic conditions, the existence of which the present investigation denies.

The curves (Fig. 6, overleaf) reproduced from Ogston and Stanier (1953) are those of the relative viscosity of synovial fluid in different concentrations against velocity gradient. Tanner (1959) has shown that the velocity gradient in the human hip joint walking at 4 m.p.h., calculated for a film thickness of 1/1,000 in., will lie at that part of the graph where synovial fluid is acting as a thin Newtonian liquid, in the region corresponding to a shear rate of 2,500 s^{-1}. Thus, while it is possible that the property of synovial fluid in providing strong films may have some action in stationary joints under load, there are no grounds for believing that this explains the low friction of a joint in motion.

The protagonists of synovial fluid as a special lubricant subserving the theory of hydrodynamic lubrication appear to dismiss as unimportant the fact that Ropes, Robertson, Rossmeisl, Peabody, and Bauer (1947) found no lubricating properties when synovial fluid was tested dynamically in an artificial joint made of Perspex. This fact seemed so important that it was decided to re-examine this aspect of the problem, and for this purpose an artificial joint was constructed, having the basic shape and average dimensions of an adult ankle-

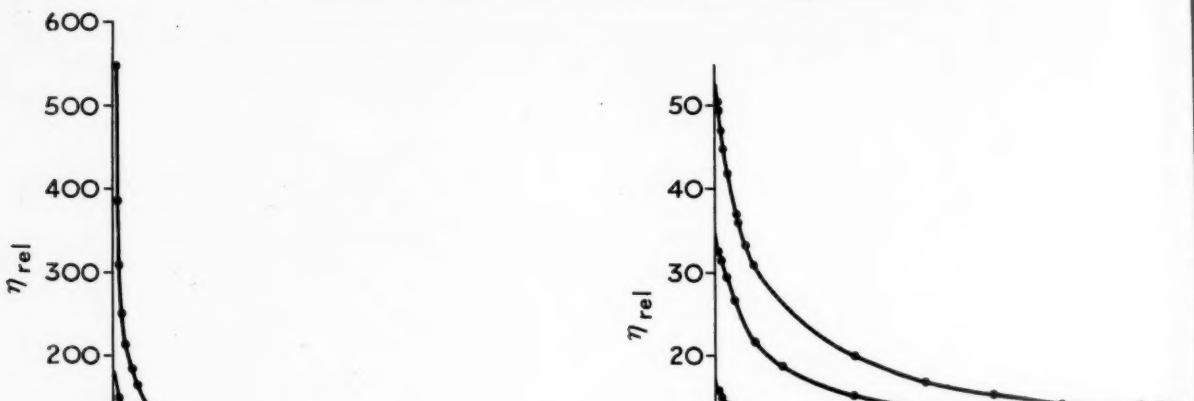

Fig. 6.—Rate of shear of ox synovial fluid at different concentrations, showing non-Newtonian behaviour at velocity gradients under s-1. (*Inst. mech. Eng.*, Proceedings of Symposium on Biomechanics, April 17, 1959, Fig. 25; *J. Physiol.* (1953), **119**, 244, Fig. 6, Ogston and Stanier.)

joint. The results of these experiments showed that synovial fluid was unable to establish and maintain a full film by the mechanism of hydrodynamic lubrication. Synovial fluid was only slightly superior to thin paraffin oil in its ability to maintain á film; after a few swings of the pendulum all the fluid was expelled and the metallic surfaces came into contact and were in danger of becoming heavily scored.

It was interesting to observe that even with the thickest lubricating oils this artificial ankle-joint with dimensions equal to that of a human subject could not establish permanently a full film under a load less than half the weight of an adult at a rate corresponding to walking speed.

It was particularly interesting to note that the artificial bearing used for this experiment was lapped to a fit of 1/10,000 in.: my engineering colleagues insisted on this degree of accuracy in order to give every facility for the establishment of hydrodynamic conditions. The surgical concept of the angle of the fluid wedge necessary to establish hydrodynamic lubrication is quite erroneous and the gross lack of congruity according to engineering standards encountered in an animal joint is a strong argument against hydrodynamic lubrication and in favour of boundary conditions at the point of contact.

The Synovial Sponge

From these considerations it is proposed that there are no grounds for believing that joint lubrication is an example of hydrodynamic or full-film lubrication. It has yet to be decided whether joint lubrication is pure boundary lubrication or boundary lubrication with a significant contribution of quasi-hydrodynamic lubrication from the free synovial fluid present in the joint cavity. It has already been shown that the coefficient of friction of articular cartilage is not significantly altered when the sliding surfaces are wiped free of visible wetting by synovial fluid.

Articular cartilage, which covers with a thin layer the ends of the bones forming a joint, is not a rigid structure like a journal bearing; it is a flexible, almost gelatinous, substance, which shares with synovial fluid the fact that in its composition there is more water than solid substance. If, after wiping the surfaces of the articular cartilage free of any loose synovial fluid, a fresh joint is compressed under a heavy load, a fluid apparently identical with synovial fluid will be expressed from the joint surfaces. It thus becomes impossible to decide whether the smear of synovial fluid which may be present on the joint surfaces derives from the joint cavity and is laid on the sliding surfaces, or whether it has been generated by the sliding surfaces themselves.

Ekholm and Norbäck (1951) have shown that, after a period of exercise, the articular cartilage of a joint is detectably thicker than in the resting state and that this increase in thickness is due to distension of the chondrocytes.

These facts thus give some substance to the ten-

tative idea that the free synovial fluid present under a joint may be a by-product of the rubbing surfaces and not, as has generally been assumed, an essential fluid required for the purpose of moistening the rubbing surfaces of the joint.

This idea of articular cartilage as a sponge containing in its interstices the same fluid which is free in the cavity of the joint as synovial fluid can be used to criticize the experiment advanced by Barnett (1956) in favour of the hydrodynamic theory of joint lubrication. In this experiment the knee joints of freshly-killed rabbits were exercised through a normal range of movement by an electrically-driven mechanism. The joint on one side was retained as a control and on the experimental side the joint was injected with an enzyme, hyaluronidase, which destroys the essential molecule of hyaluronic acid which is responsible for the viscosity of synovial fluid. At the end of the experiment it was found that the joint in which the viscous properties of synovial fluid had been destroyed had suffered serious mechanical damage to the sliding surfaces. From this it was concluded that joint lubrication must be hydrodynamic. The concept of articular cartilage as a sponge, sharing the properties of synovial fluid renders this experiment untenable. The enzyme hyaluronidase would destroy the articular surfaces just as it did the free synovial fluid. This experiment would have been valid if the experimental joint had been continuously irrigated with a harmless fluid such as isotonic saline; if the joint had then deteriorated this would have suggested the importance of free synovial fluid on the surface of the articulating surfaces.

Surgical Materials in Arthroplasty

There have been many mechanical studies of arthroplasties, especially in regard to the reconstruction of the hip-joint, but the frictional properties of the substances employed do not seem to have received attention. It is evident that it is not enough to study the static loads transmitted from a prosthetic replacement of the head of the femur to the stump of the neck of the femur if, as a result of frictional resistance to rotation of the prosthetic head in the acetabulum, the bond between the prosthesis and the bone is exposed to powerful torque forces tending to twist it loose. If it were possible to present a prosthetic femoral head with an acetabulum as slippery as a normal articulation, the bond between the prosthesis and the neck of the femur would be spared from twisting strains and the design of the anchorage of the prosthesis to cope with major forces in only one direction would be enormously simplified.

Using the general techniques previously outlined, experiments have been carried out to compare the coefficient of friction of a normal joint with the friction encountered between bone and the materials commonly used in arthroplasty, such as stainless steel, cobalt-chromium alloy, and polymethylmethacrylate (Perspex). Even when lubricated with ox synovial fluid, the coefficient of friction of bare bone against these artificial substances was found to be very adverse, being in the region of 0·4. It was quite easy, using the pendulum technique, to generate an audible "squeak" between bone and perspex, moistened with ox synovial fluid. This reproduced the squeak which is sometimes heard when a Judet prosthesis is placed in an eburnated, osteo-arthritic, acetabulum.

A feature of considerable interest was that, though bone moistened with synovial fluid showed very high frictional resistance against steel or Perspex, normal articular cartilage retained its remarkable low-friction property when tested against steel or Perspex. This suggested that the good results of prosthetic replacement of the femoral head, when done for fresh fractures of the femur, might be explained by the slipperiness of the cartilage lining the acetabulum, whereas the results when a prosthesis is used for osteo-arthritis of the hip are generally mediocre.

It is thus fairly obvious that the simple idea of designing an arthroplasty in which a polished metal or plastic sphere replaces the head of the femur and depends for lubrication on the hydrodynamic theory, using what synovial fluid may be available, may not function as well as if the acetabulum is lined with some substance, such as articular cartilage, which is intrinsically slippery. In searching for a suitable slippery substance (*i.e.* with low boundary friction irrespective of fluids on the surface), the substance polytetrafluorethylene (p.t.f.e.) was found to have properties rendering it highly suitable for developing in the design of an arthroplasty. Used against itself p.t.f.e. has a coefficient of friction of about 0·04 and against steel the value is very much the same. From the point of view of chemistry, it is an exceptionally inert plastic and eminently suitable for implantation into the body, and this has been tested by biological assay. The main disadvantage is that it has limited physical strength and has to be used in design as though it were a dense wax.

This material has been used in arthroplasty of the hip at the Centre for Hip Surgery at Wrightington, and at the Manchester Royal Infirmary, for nearly 3 years and, though the prototype designs have been superseded by recent improvements as a result of

further experience, the whole course of the investigation, covering some sixty operations, confirms the value of the basic idea. Using a prosthetic replacement of the femoral head articulating with a low-friction lining of p.t.f.e. for the acetabulum (Fig. 7), enough experience has been acquired to enable the following claims to be made for the procedure:

(1) Absolute relief from pain.
(2) Excellent freedom of motion without spasm.
(3) Final range of motion dependent solely on the range before the operation.
(4) Striking absence of new bone formation without loss of the range of motion initially obtained by the operation.

It is as yet too early to make any pronouncement on the final average ability for full weight-bearing without the assistance of sticks. Patients have so far been selected from the category of hopelessly disabled, and full activity has frequently been limited by disease in other joints. In this respect the operation has been of real value to patients with rheumatoid arthritis to whom freedom from pain and joint mobility has been a great boon, even if permanent dependence on crutches or sticks still has to be accepted. We have no doubt of the great value of this procedure in patients with rheumatoid arthritis, even when extensive osteoporosis is present, and the reservations at the moment concern its suitability for osteo-arthritis of the hip in those robust patients for whom alternative, well-tried, methods are still available albeit with the frequent penalty of stiffening, or partial stiffening, the hip.

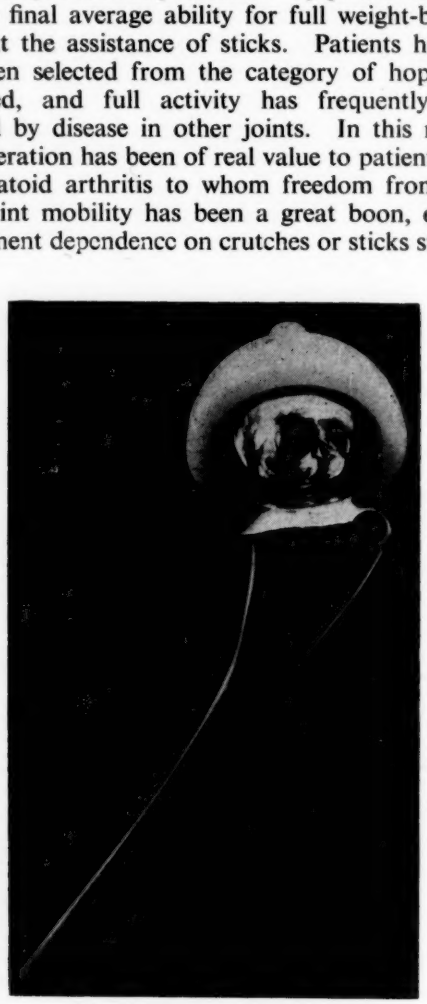

Fig. 7.—Stainless steel femoral head prosthesis (Moore type) mated with socket of p.t.f.e. used to line the arthritic acetabulum. This is the combination which it is considered can be developed in the treatment of rheumatoid arthritis to give results superior to those obtained by any of the routine methods of hip arthroplasty previously available.

Summary

This paper is a critical review of published work on the nature of lubrication in animal joints. Certain experiments which have been accepted in support of the theory of hydrodynamic lubrication have been repeated to show that the lubrication of animal joints is almost certainly a boundary phenomenon. It is emphasized that the coefficient of friction in animal joints reaches an astonishingly low figure and surpasses in slipperiness any combination of sliding surfaces known to engineering science. It is deduced that attempts to reconstruct artificial joints on the hydrodynamic theory of lubrication are doomed to failure.

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Discussion.—PROF. E. G. L. BYWATERS (*Taplow*) wondered if Mr. Charnley had considered whether the hyaluronic acid protein complex could in some way modify the individual cartilage surfaces. For example, had he tried wiping the cartilage free of synovial fluid, or substituting serum for synovial fluid in the experimental preparation.

MR. CHARNLEY replied that he had found it impossible to wipe the cartilage completely dry—there was always a little more expressed from the cartilage at the point of pressure, for it seemed that normal cartilage, which was very resilient, could absorb synovial fluid in some way. Wiping the joint did not affect its coefficient of friction. In these circumstances there would be little point in testing other substances such as serum as "lubricants".

DR. C. R. L'ESTRANGE ORME (*Parkstone, Dorset*) wondered if enough attention had been paid to the artificial conditions of the experiment, for example the exposure to drying, and the absence of blood supply.

MR. CHARNLEY reminded the speaker that the cartilage had no circulation, at least not in the form of a red blood supply. The joints used in these experiments had been kept refrigerated until required, and the observations had been made soon after opening. There had been no noticeable drying off.

DR. J. BALL (*Manchester*) asked whether the high coefficient of lubrication was a function of the whole depth of the cartilage or of the surface layer only.

MR. CHARNLEY replied that the former was probably true.

DR. H. F. WEST (*Sheffield*) said that he had tried some silicones as lubricants in joints but they had lost their lubricating properties when mixed with synovial fluid. He had also tried pure graphite—this had disappeared through phagocytosis. Subsequently (1951) he had tried ground-up polytetrafluoro-ethylene (P.T.F.E.)—it had a rather spicular appearance—in rats, but he had given this up because lesions developed that looked sarcomatous.

MR. CHARNLEY thought that there would be no engineering equivalent to the use of a powder in this way for lubricating a joint. During 2½ years' experience of its use in surgery, one or two prostheses had been taken out because of mechanical defects. Polytetrafluorethylene was the most inert plastic known, and there had been no evidence of changes in the tissue to cause alarm.

Lubrification des articulations animales

RÉSUMÉ

On présente une revue critique des travaux publiés sur la nature de la lubrification des articulations animales. Certaines expériences, servant d'appui à la thérie hydrodynamique, furent répétées. La lubrification des articulations animales est presque certainement un phénomène "limitrophe" (*boundary lubrication*, Bowden and Tabor, 1956) impliquant une affinité chimique entre le lubrifiant et les surfaces glissantes. On souligne le fait que le coëfficient de friction atteint dans les articulations animales des chiffres étonnamment bas et que ces articlations surpassent en facilité de glissement toutes les combinaisons de surfaces de glissement connues en mécanique. On en déduit que toutes les tentatives de créer des articulations artificielles à base de la théorie hydrodynamique de lubrification sont vouées à l'échec.

Lubricación en las articulaciones animales

SUMARIO

Este artículo es una revista crítica de los trabajos publicados sobre la naturaleza de la lubricación en las articulaciones animales. Ciertos experimentos, que son aceptados en sostén de la teoría hidrodinámica fueron repetidos. La lubricación en las articulaciones animales es casi con certeza un fenómeno "limítrofe" (*boundary lubrication*, Bowden and Tabor, 1956), implicando una afinidad química entre el lubrificante y las superficies deslizantes. Se resalta que el coeficiente de fricción alcanza en las articulaciones animales una cifra asombrosamente baja y que las articulaciones sobrepasan en facilidad de deslizamiento todas las combinaciones de superficies deslizantes conocidas en mecánica. Se deduce que todos los intentos de reproducir articulaciones artificiales a base de la teoría de la lubricación hidrodinámica están condenados al fracaso.

Ann. rheum. Dis. (1960) **19**, 20.

BENIGN POLYARTHRITIS*

BY

J. S. LAWRENCE AND P. H. BENNETT

From the Empire Rheumatism Council Field Unit, University of Manchester

In a recent survey of rheumatism in persons between the ages of 55 and 64 in an urban population (Kellgren and Lawrence, 1956), it was found that 36 out of the total 380 persons examined gave a past history of a transient inflammatory polyarthritis. Though carrying eventually a good prognosis, this form of polyarthritis was responsible for considerable incapacity at the time of the attack and it therefore seemed important that more information should be available on its nature and causes. Some of these patients had undoubted rheumatic fever, but there was no indication as to how many could justifiably be included in this category.

To study this and many other problems, the urban population survey mentioned above, was extended during the years 1956-59 to include all ages from 15 onwards.

Method of Sampling

In the 1956-59 survey, a 1 in 30 sample of households in the town of Leigh was used. The method of sampling was to pick from the electoral roll initially, every 360th household, giving a total of 42 houses. To these were added the inmates of the house five doors along in either direction, giving a total of 126 households. This method of "clustering", facilitated visiting without introducing factors which might arise from taking adjacent houses.

Each of the houses so chosen was visited by a medico-social worker following an initial explanatory letter and all those between the ages of 15 and 54 and from 65 onwards were invited to attend an *x*-ray centre which was set up in the school-hall. Those unable or unwilling to attend were examined by the physician at home when *x* rays were taken by means of a portable set. Where the household had moved to another town since the last electoral roll was compiled, the new occupants of the house were substituted. When 85 per cent. of the initial sample had been examined, a new sample of 126 households was chosen and examined in the same way up to 85 per cent completion, and this was repeated till over 200 persons had been examined in each decade up to age 54. The numbers in the older age groups were of course, smaller.

Examination

A history was taken of all symptoms, whether rheumatic or not, but particular attention was paid to incapacitating musculo-skeletal disorders. Incapacity was graded according to the number of weeks lost from work. In the case of housewives or retired persons, confinement to the home was substituted. All those attending the centre were submitted to a detailed examination of the skeletal system and the blood pressure was taken. In those with a history of past polyarthritis, the heart was examined. In addition, in all persons a sample of blood was drawn for the sheep-cell test which was assessed by the method of Ball (1950). Radiographs were taken according to the following scheme, designed to reduce radiation genetic hazards to a minimum.

Age (yrs)	Parts *x*-rayed
–34	Hands, feet, and cervical spine
–54	Hands, feet, and cervical spine, lumbar spine, and knees
55+	Hands, feet, cervical and lumbar spine, knees, and pelvis

Antero-posterior views only were taken of the hands, feet, knees, and pelvis, and lateral views only of the spine. During the first half of the survey, a routine *x* ray of the chest and in the latter half, of the dorsal spine was included. The chest was

* Paper read to the Heberden Society in December, 1959.

x-rayed in those with a history of past polyarthritis throughout the survey.

Completeness of Survey

For the present studies, a 1 in 2 sample of persons between the ages of 55 and 64 from the 1954 survey, stratified by clinical rheumatoid grading, has been added to give a complete age range from 15 onwards. When these had been added to the total, the sample comprised 751 males and 814 females of whom 653 males and 690 females were *x*-rayed or had a blood test giving a completion rate of 87 and 85 per cent. respectively (Table I). Some of the remainder had a clinical examination only. These have not been included in assessing the completion rate.

Prevalence

A past history of polyarthritis was encountered in 34 males and fifty females, 5 and 7 per cent. respectively of the total examined in each sex (Table II). The proportion giving a history of this type rose with age in females but showed no constant age correlation in males. Seven males and fifteen females showed residual evidence of arthritis either clinically or radiologically in the form of erosive arthritis. Osteo-arthrosis was not included amongst the residua but will be considered later. Arthritic residua were thus encountered in 26 per cent. of persons with a history of polyarthritis. None of those below age 35 had residua, but above this age there was no striking relationship with age.

The clinical residua are analysed in detail in

TABLE I

COMPLETENESS OF SURVEY

Sex	Age (yrs)	Total in Sample	Not Available or Refused All Examination	Total Examined	Completion Rate (per cent.)	Clinical Examination, *X* Ray and Blood Test	Clinical Examination, and *X* Ray Only	Clinical Examination, and Blood Test Only
Male	–24	125	20	105	83	97	1	7
	–34	131	12	119	91	112	6	1
	–44	127	20	107	84	102	4	1
	–54	169	18	151	89	147	4	0
	–64	102	9	93	91	87	5	1
	–74	65	10	55	84	50	2	3
	75+	26	3	23	88	21	1	1
	Not stated	6	6					
	Total ..	751	98	653	87	616	23	14
Female	–24	122	16	106	86	95	3	8
	–34	115	9	106	92	98	6	2
	–44	148	24	124	84	119	5	0
	–54	171	19	152	89	139	12	1
	–64	138	26	112	81	100	11	1
	–74	81	18	63	78	53	9	1
	75+	34	7	27	79	19	3	5
	Not stated	5	5					
	Total ..	814	124	690	85	623	49	18

N.B.—A number of persons aged 15–24 yrs had *x* rays of the dorsal spine only. These are included in the last column (Clinical Examination and Blood Test Only) because their *x* rays were incomplete.

TABLE II

PREVALENCE OF PAST POLYARTHRITIS BY AGE AND SEX

Age (yrs)	Males					Females					Both	
	Total in Sample	Total Examined	Past Polyarthritis			Total in Sample	Total Examined	Past Polyarthritis			Past Polyarthritis	
			Total		With Residua			Total		With Residua	Total	Percentage with Residua
			No.	Per cent.				No.	Per cent.			
–24	125	105	6	6	0	122	106	4	4	0	10	0
–34	131	119	4	3	0	115	106	5	5	0	9	0
–44	127	107	4	4	2	148	124	7	6	4	11	50
–54	169	151	6	4	0	171	152	13	9	3	19	16
–64	102	93	10	11	3	139	112	11	10	2	21	24
65+	91	78	4	5	2	115	90	10	11	6	14	71
Total ..	745	653	34	5	7	753	690	50	7	15	84	26

Table III, comparison being made with those persons in the sample who gave no history of polyarthritis. Clinical residua were found in 9 per cent. of males with a past history of polyarthritis but in only 2 per cent. of those without such a history. In females, the proportions were 24 per cent. and 4 per cent. respectively. Differences in age distribution could not account for these differences. Not only were clinical residua five times as common in those with a past history, but they appeared at an earlier age, the peak prevalence being at age 35 to 44 compared with a peak at age 55 to 64 in those without a history of past polyarthritis.

Clinical residua included subluxation in the interphalangeal and metatarsophalangeal joints, and pain or limitation of movement of the metacarpophalangeal joints, wrists, knees, tarsal joints, and cervical spine. One patient gave a history of recurrent tendon sheath swellings. Three patients had frank rheumatoid arthritis, but only one of these had a positive sheep-cell agglutination test.

Radiological residua (Table IV) were also more frequent in persons with a past history of polyarthritis, particularly in the cervical spine, only slightly in the hands and feet. Indeed, there was radiological evidence of erosive arthritis in these sites in only three persons with a past history of polyarthritis. In no instance was there definite evidence of erosive arthritis in the sacro-iliac joints. The cervical changes (Figs 1 and 2, opposite) did not appear at an earlier age in those with past polyarthritis, none being found before age 45. They differed somewhat in appearance from those encountered in persons with rheumatoid arthritis (Sharp, Purser, and Lawrence, 1958). Subluxation was a less striking feature and degenerative changes were more marked. These differed, however, from appearances in simple disk degeneration in that the upper cervical disks were affected more than the lower. There was no evidence of growth defect in the cervical spine and indeed, only two of those with cervical changes had their attack of polyarthritis before age 55, so that cervical involvement would appear to be a feature mainly of late polyarthritis. No definite spondylitis was encountered in any of these persons with a history of polyarthritis.

TABLE III

CLINICAL RESIDUA OF INFLAMMATORY ARTHRITIS IN PERSONS WITH AND WITHOUT A PAST HISTORY OF POLYARTHRITIS, BY SEX AND AGE

Age (yrs)	Males									Females								
	Past Polyarthritis				No Past Polyarthritis				Past Polyarthritis				No Past Polyarthritis					
	Total	Grade		Grade 2–4	Total	Grade		Grade 2–4	Total	Grade		Grade 2–4	Total	Grade		Grade 2–4
		0 1	2 3 4			0 1	2 3 4			0 1	2 3 4			0 1	2 3 4	
–24	6	5 1	— — —	0	99	96 3	— — —	0	4	2 2	— — —	0	102	96 6	— — —	0
–34	4	4 —	— — —	0	115	107 6	1 1 —	0·02	5	5 —	— — —	0	101	91 7	3 — —	0·03
–44	4	1 1	2 — —	0·5	103	101 2	— — —	0	7	1 2	4 — —	0·6	117	101 13	3 — —	0·03
–54	6	5 1	— — —	0	145	133 7	4 1 —	0·04	13	2 9	1 1 —	0·2	139	118 19	2 — —	0·01
–64	10	8 1	— — 1	0·1	83	78 4	1 — —	0·01	11	8 1	1 1 —	0·2	101	76 12	10 1 2	0·13
65+	4	1 3	— — —	0	74	70 2	— 1 1	0·03	10	4 2	4 — —	0·4	80	65 10	1 3 1	0·06
Total	34	24 7	2 — 1	9 per cent.	619	583 24	6 3 1	2 per cent.	50	22 16	10 2 —	24 per cent.	640	547 67	19 4 3	4 per cent.
Equivalent Average Morbidity (per cent.)				10				2				22				4

TABLE IV

RADIOLOGICAL RESIDUA IN PERSONS WITH AND WITHOUT A PAST HISTORY OF POLYARTHRITIS, BY SEX

Residua	Males								Females							
	Past Polyarthritis				No Past Polyarthritis				Past Polyarthritis				No Past Polyarthritis			
	Total	Grade		Percentage Grade 2–4	Total	Grade		Percentage Grade 2–4	Total	Grade		Percentage Grade 2–4	Total	Grade		
		0 1	2 3 4 N.S.			0 1	2 3 4 N.S.			0 1	2 3 4 N.S.			0 1	2 3 4 N.S.	
Hands and Feet	34	27 6	1 0 0 0	3	619	513 68	13 4 0 21	3	50	38 9	2 0 0 1	4	640	512 86	11 1 3 27	
Cervical ..	34	28 1	3 0 0 2	9	619	472 100	19 1 0 26	3	50	35 9	5 0 0 1	10	640	487 90	21 4 0 38	

Fig. 1.—Cervical spine in female aged 77 with past history of polyarthritis. Ankylosis of apophyseal joint C.3-4 with narrowing of disk.

Fig. 2.—Cervical spine in male aged 65 with past history of polyarthritis. Narrowing of disk C.3-4 with proliferation. Anterior subluxation at disk C.2-3 and posterior subluxation at disks C.3-4 and 4-5.

Sheep-cell Agglutination Test.—The sheep-cell test (Table V) was positive in two males (6 per cent.) and four females (9 per cent.) with a past history of polyarthritis. This may be compared with figures of 5 and 6 per cent. in males and females without such a history. Neither of these differences is significant. A study of the titre distribution shows that three of the four females with a history of polyarthritis and a positive sheep-cell test had a titre of 1 in 64 or over, whereas only one-third of the sero-positive females without polyarthritis had such a high titre. This difference, however, is also not significant and in males the reverse holds, there being no positive titres above 1 in 32 in those with a past history of polyarthritis. Of the four sero-positive females, three had clinical residua, the fourth gave a history of pain and swelling of her knees

TABLE V

SHEEP-CELL AGGLUTINATION TITRE IN PERSONS WITH AND WITHOUT PAST HISTORY OF POLYARTHRITIS, BY SEX

Sex	Total	S.C.A.T. Titre ..	0	4	8	16	32	64	128	256	512	Not Tested	Percentage 32 and Over
Male	34	Past Polyarthritis ..	18	5	6	2	2	0	0	0	0	1	6
	619	No Past Polyarthritis	363	111	62	30	12	8	7	3	1	22	5
Female	50	Past Polyarthritis ..	26	7	6	3	1	1	0	2	0	4	9
	640	No Past Polyarthritis	339	108	72	41	22	3	6	1	1	47	6

3 months previously. She refused to allow a clinical examination of her knees or feet but had no clinical evidence of the disease elsewhere. The two males with a positive test both had radiological evidence of erosive arthritis in the cervical spine but neither had definite clinical residua.

Cardiac Residua.—A history of cardiac involvement at the time of the attack was given by seven males and seven females (17 per cent.), but only four of these (two males and two females) had clinical evidence of mitral stenosis in the form of an apical presystolic murmur. In none was there evidence of aortic involvement. One patient had auricular fibrillation but was hypertensive, another an apical systolic murmur with slight prominence of the pulmonary conus on *x* ray and may possibly have had mitral valvular disease with regurgitation.

A chest *x* ray was made in 22 of the males and 23 of the females with a history of polyarthritis. Only one of those with mitral stenosis was able to attend for chest *x* ray but in this one the diagnosis was confirmed. No other showed evidence of mitral disease on *x* ray.

Enlargement of the left ventricle was noted in two males and one female. Only the female had a raised blood pressure. In the two males no cause for the left ventricular enlargement was found.

Age at Onset.—In both sexes the onset was most frequent between the ages of 5 and 24, some 60 per cent. arising between these ages (Table VI). In only one did the attack start before age 5, actually at age 3. After age 24, the incidence fell sharply, and in only nine (11 per cent.) did the condition appear after age 44. This variation in age incidence is partly but not wholly, due to the smaller numbers in whom the disease could have occurred in later decades. The age distribution is in general that of rheumatic fever. Those with residua tended to have their onset rather later in life, some 50 per cent. appearing between the ages of 5 and 24 and 20 per cent. after age 44. Those with cardiac residua on the other hand all had their attack between the ages of 5 and 24.

Season of Onset.—Of the 84 persons with a history of past polyarthritis, 25 were unable to remember at what season the attack arose. Eleven were able only to remember whether the attack occurred in winter, spring, summer, or autumn, but the remainder could recall within a month or two the date of onset. In this last group, the illness started most commonly between January and March and least often between May and August (Fig. 3, opposite). Those with residua had a less striking seasonal incidence than the remainder.

The monthly incidence indicates a rather earlier onset than in rheumatic fever (as shown by the data of Coburn and Young, 1949), in which the maximum is attained in March and the minimum in September (Fig. 3). It does, however, fit remarkably closely the data given by Short, Bauer, and Reynolds (1957) for exacerbation of rheumatoid arthritis.

Year of Onset.—A study of the years in which these attacks occurred has been made and is shown in Table VII (overleaf). Only those attacks starting before 1954, when the survey started, are included. The first attack occurred in 1885, the last in 1954. They were fairly evenly distributed over the intervening years, the largest number in any one year being four. The condition thus appeared to be endemic rather than epidemic. The highest proportion (3 per cent. of those living at that time) was found in the 1905 to 1914 decade. There was no evidence that the condition is becoming less frequent though its nature appears to be changing. Those with mitral stenosis all had had their attack of polyarthritis before 1918 and, of those with a history of heart

TABLE VI

AGE AT ONSET OF POLYARTHRITIS, BY SEX

Age at Onset (yrs)	Males			Females			Both Sexes			
	Total Liable	Past Polyarthritis		Total Liable	Past Polyarthritis		Past Polyarthritis			
		Total	With Residua		Total	With Residua	Total		With Residua	
							No.	Per cent.	No.	Per cent.
– 4	653	0	0	690	1	0	1	0·07	0	0
–14	653	11	2	690	16	4	27	2	6	0·4
–24	653	11	1	690	15	4	26	2	5	0·4
–34	548	5	1	584	7	2	12	1	3	0·3
–44	429	3	2	478	6	1	9	0·9	3	0·3
–54	322	2	0	354	4	3	6	0·9	3	0·4
–64	171	2	1	202	1	1	3	0·8	2	0·6
65+	78	0	0	90	0	0	0	0	0	0
Total	.. ..	34	7		50	15	84		22	

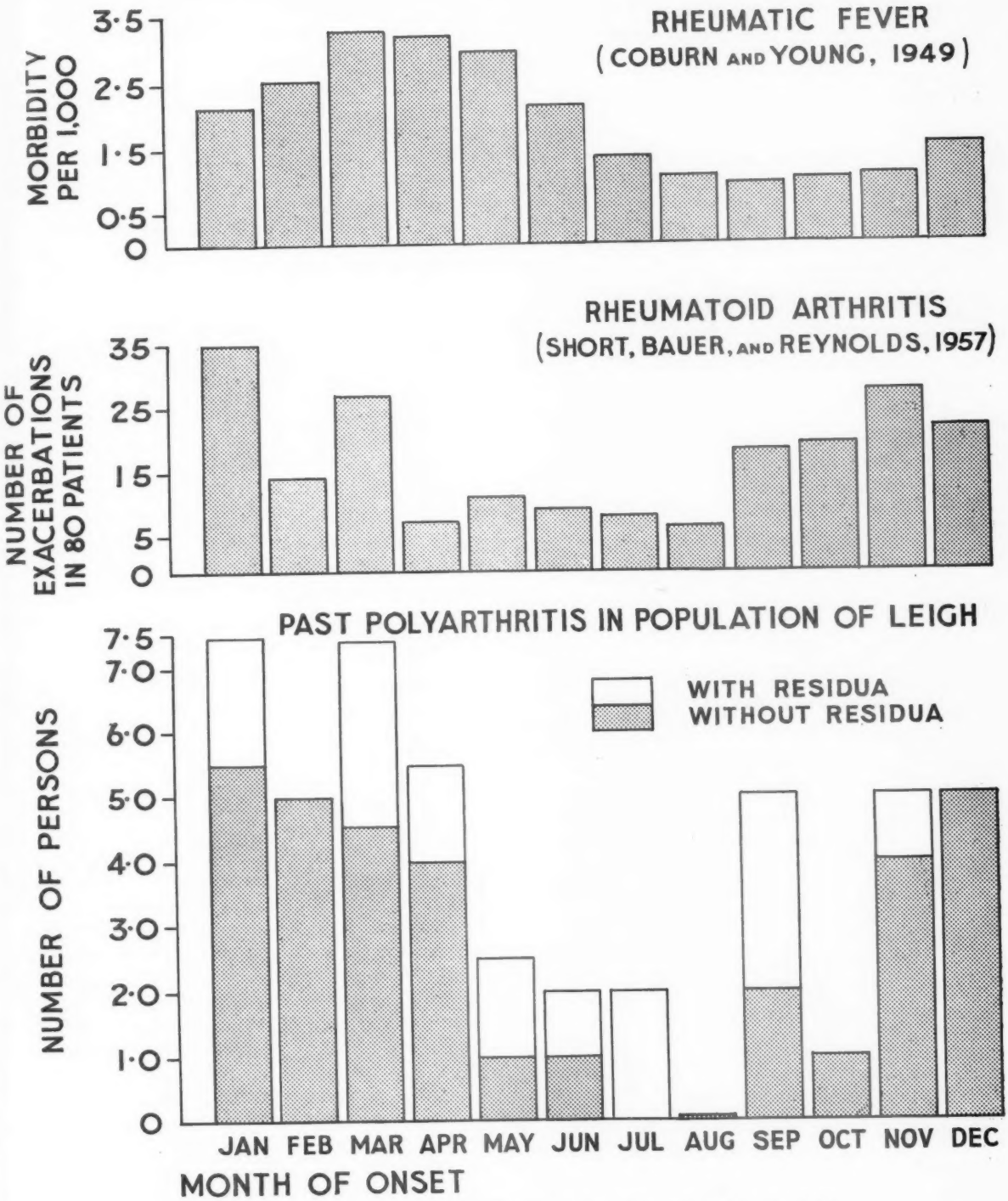

Fig. 3.—Season of onset of rheumatic fever, rheumatoid arthritis, and benign polyarthritis.

TABLE VII

YEAR OF ONSET OF POLYARTHRITIS

Year of Onset	Total Available	Past Polyarthritis							
		Total		With Rheumatic Heart Disease				With Arthritic Residua	
				History Only		Mitral Stenosis			
		No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
1885–1904	373	2	0·5	2	0·5	1	0·3	2	0·5
–1914	676	18	2·7	4	0·6	1	0·1	3	0·4
–1924	907	12	1·3	2	0·2	2	0·2	4	0·4
–1934	1,132	16	1·4	4	0·4	0	0	7	0·6
–1944	1,343	18	1·3	1	0·07	0	0	4	0·4
–1954	1,343	16	1·2	0	0	0	0	2	0·1

involvement, only one had his attack after 1934. The number of persons with polyarthritis associated with arthritic residua remained fairly constant except in those whose attacks occurred after 1944, of whom only two had arthritic residua. This may be because residua have not become apparent for example on *x* ray particularly in the spine. It would seem unlikely that this could explain the lower prevalence of cardiac residua in the more recent attacks.

Association with Other Rheumatic Diseases.—The possibility that this type of polyarthritis might produce a tendency to degenerative joint disease later, has been considered. Of the 34 males with past history of polyarthritis, three (14 per cent.) were found to have osteo-arthrosis in four or more groups of joints* compared with 59 (10 per cent.) in the remainder of the males. For the females, the figures were fourteen (25 per cent.) and 88 (14 per cent.) respectively. When these figures were corrected for age, the differences were much reduced, 13 and 12 per cent. respectively for males and 21 and 16 per cent. for females. Thus there is no significant increase in osteo-arthrosis in later life in persons with a history of polyarthritis though there may be a slight predisposition in females.

No significant increase was found in the amount of intervertebral disk degeneration in persons with a history of polyarthritis, though there was a tendency towards more frequent involvement of cervical and dorsal disks in males and of lumbar disks in females.

Regional Prevalence.—In addition to the population of Leigh, other populations have been examined, notably in Wensleydale and in the Rhondda Fach and Vale of Glamorgan in South Wales. Only in Wensleydale have all age groups been examined, and here the proportion of persons who had had an attack of polyarthritis was very similar to that found in Leigh, 6 per cent in males and 8 per cent. in females (Table VIII). In South Wales the prevalence was 6 and 12 per cent. respectively. Only the 55 to 64 age group was examined in the females in South Wales and the figure was thus very similar to the 10 and 12 per cent. prevalence in Leigh and Wensleydale in females in this age group.

TABLE VIII

PAST POLYARTHRITIS IN DIFFERENT AREAS, BY SEX

Area	Males			Females		
	Total	Polyarthritic		Total	Polyarthritic	
		No.	Per cent.		No.	Per cent.
Leigh	653	34	5	690	50	7
Wensleydale ..	393	22	6	479	39	8
South Wales ..	527	34	6	268	33	12

Discussion

In the past, it has been customary to include all acute self-limiting polyarthritis under the category of rheumatic fever and no doubt in most instances this was correct. It was, however, recognized that in a few cases classical rheumatoid arthritis subsequently developed. It is probably true today that most of the patients admitted to hospital with acute febrile polyarthritis are in fact cases of rheumatic fever.

Cardiac abnormalities have been found in from 51 to 74 per cent. of patients having rheumatic fever in childhood though in only 17 to 24 per cent. of those attacked in adult life (Engleman, Hollister, and Kolb, 1954).

Patients in the present series were almost all treated at home and, therefore, presumably included many milder forms not commonly seen in hospital practice. This might account for the low pre-

* For this purpose all distal interphalangeal joints of the fingers, for example, were considered as one.

valence of cardiac abnormalities. Moreover, a certain number of persons who had rheumatic fever in the households under review will have died before 1954, and will thus have been omitted from the survey. It is impossible to know how many were excluded in this way. In a series of 1,000 cases of rheumatic fever followed for 10 years (Schlesinger, 1938), 12 per cent. had died, the mortality falling off rapidly after age 14. From the Registrar General's figures for 1940-49, it would be expected that some eighteen persons would have died in a population sample of the size used in this study over the period of 70 years which it covers. Thus the original sample might have been 102 of whom 22 developed heart disease and eighteen died.

Arthritic residua were found in 23 of the 84 survivors and it would thus appear that at least as many of the original cases developed arthritic as cardiac residua. This proportion is likely to be changing however. Admissions to Great Ormond Street Hospital for acute rheumatism have fallen from 216 to 25 in the last 50 years (Sheldon, 1958). The Registrar General's figures for England and Wales, moreover, show a steady decline in mortality from rheumatic fever from 1,251 in 1940 to 208 in 1956, and a similar reduction is occurring in other countries (Southwood, 1959). The figures shown in Table VII indicate that there is a corresponding reduction in the proportion of attacks of polyarthritis which are associated with cardiac complications and it may well be that almost as many attacks occurring at the present time in the population are not rheumatic fever but belong to some relatively benign form of polyarthritis.

What is the nature of this condition? The onset is commonly between the ages of 5 and 24. It is only slightly commoner in females. Attacks occur chiefly between January and March. The attack is usually single, but as many as nine attacks have occurred in one person. As would be expected, residua are more common in those who have had repeated attacks. The attack commonly lasts 2 to 3 months but some patients have been away from school or work for over a year. On the other hand twelve (14 per cent.) were able to continue their occupation throughout.

Because of the lapse of time, it was often difficult to elicit a detailed account of the illness. A prodromal throat infection was remembered by only a few. Many recalled only having pain all over and sweating profusely. A common sequence, however, was pain which started in the feet and spread to the ankles and knees and sometimes to the hands with or without joint swelling. Often the upper extremities had apparently remained quite unaffected. Severe pain in the back, neck, and shoulders was often mentioned in addition to peripheral pain.

Several possibilities must be considered in discussing the nature of this benign form of polyarthritis. The age at onset and the rheumatoid nature of the arthritic residua suggests that many would fall into the category of Still's disease, a diagnosis which cannot be altogether excluded by the favourable outcome. In the series of 200 cases of Still's disease followed by Ansell and Bywaters (1959), the disease became inactive in 95, and in 44 per cent. of early cases there were no joint residua. As in the present cases, the cervical spine has been found to be a frequent site of radiological change, but the diminished width of vertebral bodies commonly found in patients who have had Still's disease was not seen in the present series and the acute course of the polyarthritis is not typical.

Many of those in whom the condition occurred in adult life would, in the less acute forms, have been diagnosed as cases of rheumatoid arthritis. The relatively benign course of adult polyarthritis in which the sheep-cell test is negative has been stressed by Duthie, Brown, Knox, and Thompson (1957). It cannot be known what the sheep-cell titre may have been at the time of the attack in the present series. In some instances the test is known to change from positive to negative in rheumatoid patients. In others, however, the change is in the reverse direction. Had an appreciable proportion of patients in the present series been sheep-cell positive during the attack, there would surely have been a significantly higher proportion of positives in the polyarthritics than in the remainder of the population.

The joint residua found in these patients do not resemble those described by Jaccoud (1869), Bach (1935), and Bywaters (1950) in patients with rheumatic heart disease. The predominant involvement of the metacarpophalangeal joints of the hands with ulnar deviation and hook erosions was not seen in these patients. Moreover, these changes are usually considered to be rare, even in patients who have had a severe attack of rheumatic fever.

Attacks of polyarthritis have been noted by Hollister and Engleman (1958) as a frequent precursor of spondylitis. As no patients in this series later developed spondylitis this would not seem to be a likely explanation.

Leu (1954) has described a condition which he has labelled "abortive acute polyarthritis". This condition appeared in the early months of the year but was otherwise unlike the present series, constitutional upset being slight and the temperature

normal. Some may, however, have belonged to this category.

The polyarthritis described in this paper bears no resemblance to palindromic rheumatism, in which the arthritis is more transient and commonly affects only one joint at a time, but many would fall into the category of "subacute" rheumatism described by Newman (1924) in his survey of rheumatic diseases. Three females and two males gave a history of skin lesions consistent with a diagnosis of erythema nodosum. Only one of these had joint residua and in this person the sheep-cell test was strongly positive.

No definite views on causation can be expressed on the evidence available. The seasonal onset would suggest that, in some individuals, attacks of this kind may be related to one or more of the infectious diseases which are prevalent in the first 3 months of the year. The similarity between the seasonal onset of benign polyarthritis and of exacerbations of rheumatoid arthritis further suggest that the same infections may trigger the rheumatoid exacerbation in persons so predisposed.

In clinical experience, benign forms of polyarthritis are not uncommonly associated with viral diseases. Polyarthritis occurring as a complication in epidemics of rubella has been described by Geiger (1918), Hope Simpson (1940), Bennett and Copeman (1940), Loudon (1953), and Lewis (1954). A notable feature is that adults are mainly affected, females more than males, and that the attack is often associated with eye symptoms—redness, photophobia, and lacrimation. According to Johnson and Hall (1958), the latex test is negative on whole serum, but a positive inhibition test is found in nine out of ten patients with rubella arthritis. Lloyd (personal communication) has encountered several cases of arthritis occurring in an epidemic of measles, and it has also been observed in infective hepatitis.

Summary

During a survey of rheumatic disease in a random population sample of persons aged 15 years and over in the town of Leigh, 5 per cent. of males and 7 per cent. of females gave a past history of one or more attacks of polyarthritis.

Of the 84 persons giving such a history, only four had definite clinical or radiological evidence of rheumatic heart disease, but 23 had joint residua. Both clinically and radiologically, these patients had more evidence of inflammatory joint residua than the remainder of the population, but the sheep-cell agglutination test was positive in only 7 per cent. Radiological changes were found chiefly in the cervical spine and resembled, but were not typical of, those found in rheumatoid arthritis.

Attacks were most frequent in the winter months and were sometimes recurrent. The onset was commonly between the ages of 5 and 24, but might occur at any age, the oldest patient being 63 years old. Patients were seldom admitted to hospital.

It is suggested that many cases of acute and subacute rheumatism fall into a category of benign polyarthritis related to the sheep-cell negative group of inflammatory polyarthritis.

We are indebted to Professor J. H. Kellgren for his advice and to Dr. J. Ball for estimating the sheep-cell test.

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DISCUSSION

DR. W. R. M. ALEXANDER (*Edinburgh*) asked whether there was any history of erythema nodosum in these patients, and secondly, although the sheep cell test was negative at the time of the survey, whether the author could be certain that it was negative at the time of the polyarthritis? Some patients with acute polyarthritis might have a positive sheep cell test which later became negative.

DR. H. F. WEST (*Sheffield*) said that it was his impression that this was a familiar picture. The patients arrived after about one month, with a history of an upper respiratory infection. After returning to work they had developed an acute polyarthritis. They were

usually young adults and the chances were that the arthritis would clear within 6 months. Their hearts were examined and an attempt was made to assess whether they were to be treated as cases of rheumatic fever and whether they needed a strict regimen of rest in bed.

DR. K. LLOYD (*Cardiff*) said that about 4 years earlier he had seen many cases of acute polyarthritis developing about the tenth day of measles, lasting for 3 or 4 weeks, and leaving no residua. He did not know whether there had been any other unusual features of the measles epidemic that year, or to what extent there might be a link between the higher rate of illness in winter and spring and cases of polyarthritis with no residua.

PROF. E. G. L. BYWATERS (*London*) said that he used to call this condition "doctors' wives' syndrome", because the cases presented early. It was not a single syndrome, but most types of arthritis had abortive specimens among them, which might abort within a day or two of the onset. It was not possible to define these fleeting polyarthritic attacks very closely as they might easily fit a variety of conditions. He asked whether the sacro-iliac joints showed any changes.

DR. O. SAVAGE (*London*) said that the condition was not uncommon, and that a negative Rose-Waaler test was often seen in rheumatoid arthritis of less than one year's duration.

DR. M. THOMPSON (*Newcastle-upon-Tyne*) recalled that Dr. Lloyd had mentioned polyarthritis complicating measles. A similar state of affairs was sometimes seen with German measles, especially in adult females, and polyarthritis might also be seen during and after infective hepatitis. There appeared to be many types of self-limited polyarthritis, some associated with virus infections. The ultimate answers to the definition of these various forms of acute polyarthritis would only come from prospective studies. The current study of 1,000 families in Newcastle-upon-Tyne, concerned with infants born in 1947 and 1948, might give some information of value although the numbers were small for this type of study.

DR. J. J. R. DUTHIE (*Edinburgh*) said that he had had some forty cases of this type but, far from being mild, they were so acute that all the patients concerned were admitted to hospital within the first year of their illness. Initially they all looked as if they were going rapidly downhill, but as they had a good prognosis they should not necessarily be treated with steroids.

PROF. S. J. HARTFALL (*Leeds*) observed that there had been no information about throat infections or streptococci.

DR. LAWRENCE replied that they had had five patients with a history of erythema nodosum. The sheep cell test might become negative in a recovering polyarthritis but in just as many cases it became more positive. When he had studied the population he had found an increasing prevalence of positive tests with age. He thought that if many of these people had had positive tests at the time of their polyarthritis, they would have afterwards found a greater prevalence of positive tests among them than in the rest of the population.

Attacks following measles are interesting but none of the patients in this study had volunteered a history of measles, although some said they had had a sore throat. He agreed that this was not a single syndrome. The sacro-iliac joints were only *x*-rayed in the older age groups, and no striking changes had been seen in those done. With regard to the streptococcus, only a few gave a history of preceding sore throat, but the seasonal incidence had corresponded roughly with that of streptococcal infection.

PROF. J. H. KELLGREN (*Manchester*) said that the condition described was common, and apparently involved 5 per cent. of the population, yet little had been written about it. He thought it interesting that very few patients had subsequently developed chronic polyarthritis. The whole subject of polyarthritis in relation to virus diseases was something they should know more about, and he was hoping that members of the society would collect more data.

Polyarthrite benigne

RÉSUMÉ

Au cours d'une enquête sur la maladie rhumatismale, effectuée sur une population d'essai de la ville de Leigh, comprenant des personnes âgées de 15 ans et plus, on trouva que 5% d'hommes et 7% de femmes eurent des antécédants d'une attaque au moins de polyarthrite.

Sur 84 personnes avec ces antécédants, quatre seulement présentèrent des signes cliniques et radiologiques définis de cardiopathie rhumatismale, mais 23 personnes eurent des séquelles articulaires. Du point de vue clinique et radiologique, ces personnes présentèrent plus de signes de séquelles inflammatoires articulaires que le reste de la population, mais la réaction d'agglutination des globules rouges de mouton ne fut positive qu'en 7% d'entre elles. Les altérations radiologiques se trouvèrent surtout dans la colonne cervicale et ressemblèrent, sans être typiques, à celles trouvées dans l'arthrite rhumatismale.

Les attaques survenaient le plus souvent en hiver et quelquefois tendaient à revenir. La maladie commençait généralement entre les âges de 5 à 24 ans, mais pouvait commencer à n'importe quel âge, le malade le plus vieux étant âgé de 63 ans. Admission à l'hôpital était rarement nécessaire.

On suggère que beaucoup de cas de rhumatisme aigu et subaigu appartiennent à la catégorie de polyarthrite benigne, associée au groupe de polyarthrite inflammatoire à réaction d'agglutination des globules rouges de mouton négative.

Poliartritis benigna

SUMARIO

En el curso de investigación sobre enfermedad reumática, realizada en una muestra de población no seleccionada de personas de edad superior a 15 años, en la ciudad de Leigh, se encontró que el 5% de los varones y el 7% de las mujeres referían uno o más ataques anteriores de poliartritis.

De las 84 personas con tal historia, sólo en cuatro

existían signos evidentes, clinícos y radiológicos, de cardiopatía reumática, pero 23 tenían secuelas articulares. Clínica y radiológicamente, estos enfermos presentaban más signos de secuelas inflamatorias articulares que el resto de la población, pero la reacción de aglutinación de los eritrocitos de carnero fué positiva sólo en el 7 por ciento. Las alteraciones radiológicas aparecieron principalmente en la columna cervical y se asemejaron, sin ser típicas, a las que se encuentran en la artritis reumatoide.

Los ataques aparecieron con más frecuencia durante los meses de invierno y fueron recurrentes en algunos casos. La enfermedad solía principiar entre los 5 y los 24 años, pero podía aparecer en cualquier edad, en un caso a los 63 años. Rara vez los enfermos necesitaron hospitalización.

Todo ello sugiere que muchos casos de reumatismo agudo y subagudo entran en la categoria de poliartritis benigna. entidad relacionada con el grupo de poliartritis inflamatoria con la reacción de aglutinación de los eritrocitos de carnero negativa.

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CHONDROCYTE FUNCTION OF HUMAN ARTICULAR AND COSTAL CARTILAGE COMPARED BY MEASURING THE *IN VITRO* UPTAKE OF LABELLED (^{35}S) SULPHATE

BY

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It has long been known that the joint cartilages, as age advances, tend to undergo certain changes which render them less resilient and less able to withstand injury. These have been referred to as regressive or involutionary (Collins, 1949, p. 100), but their true nature is still obscure. The gross and microscopic features of so-called age-changes in the joints have been well studied in large series of individuals by Heine (1926) and Bennett, Waine, and Bauer (1942), and they are of the same type, though varying in degree, as those seen in osteo-arthritis accompanied by symptoms or by bony deformity of the articulations. Local mechanical conditions cannot be dismissed in considering the aetiology of osteo-arthritis; if disadvantageous, they certainly accelerate the process. But apart from the occasional instance of secondary osteo-arthritis occurring in the severely injured or badly deranged joint of a young person, osteo-arthritis is a disease of the elderly, and the senescence of articular cartilage in man needs to be examined.

Some attention has been given to the chemical composition of the matrix of cartilage, but little to its cells, although upon them its vitality clearly depends. The activity of chondrocytes in the synthesis of chondroitin sulphate can be studied with radioactive sulphate, and there is now enough experience with this method to permit its use *in vitro* with human tissues, as will be explained.

Our present study uses this technique and is directed to comparing chondrocyte function in an articular cartilage (patella) with that in a non-articular cartilage (rib) in the same person. An intrinsic senescent change might affect the cartilage of the body as a whole; or a cellular failure to maintain the matrix might be apparent only in the joint cartilages. Chemical analyses of human joint cartilage in osteo-arthritis, by Hirsch (1944) and by Matthews (1953), indicate a loss of mucopolysaccharide which might well be the consequence of failing chondrocyte function. Our results, however, point to a different conclusion—that the chondrocytes of ageing articular cartilage become increasingly active in sulphate utilization, whereas those of the rib show no such trend.

Material

Large pieces of the cartilaginous portions of the 7th rib, sometimes including the articulating 8th or 9th costal cartilages, were removed at 44 necropsies on subjects ranging in age from 5 days to 83 years.

In 32 of these cases a patella was also removed and comparative studies of chondrocyte activity in rib and patellar articular cartilage were completed in 31 instances.

Ten biopsy specimens of costal cartilage were examined; these were obtained from patients aged 23 to 68 years at operation, mainly thoracotomy.

In all, 54 costal cartilages and 32 articular cartilages were examined.

Specimens were processed as soon as possible or stored at 4° C. in the incubation medium. The intervals between death and the *post mortem* examination and between the collection of the specimen and its processing were carefully noted. It was necessary to investigate the *post mortem* degradation of chondrocyte activity, but in the comparative studies of rib and patellar cartilages conditions were uniform for each pair of specimens.

Methods

Preparation of Specimens

(*a*) *Costal Cartilage.*—Portions of costal cartilage free from obvious calcification were used. Except in slices for autoradiography, the perichondrium and surrounding tissues were removed. For incubation, slices of cartilage 0·5 mm. in thickness, to give an eventual dry weight of

about 20 mg., were cut from the transverse diameter of the specimen. Some portions of costal cartilage were stored in the unsliced block at 4° C. and at room temperature in the medium, and repeated estimations were made of their ability to fix sulphate *in vitro* at 37° C.

(*b*) *Patellar Cartilage.*—The patellae were inspected, and changes of osteo-arthritis, if present, were graded O-IV according to the classification proposed by Collins (1949, p. 76). Blocks of cartilage down to the bone were removed from the complete transverse diameter of the patellae. These blocks were then sliced as finely as possible with a sharp razor. Fine slices of cartilage are said to give optimum uptake of sulphate (Boström and Månsson, 1953). The thickness of the articular cartilage on the patella ranged between 0 and 5 mm.

Incubation Medium

The medium used for incubating the specimens and in which they were transported and stored was that described by Kodicek and Loewi (1955-56). This is a salt solution containing glucose buffered to pH 7·3, to which sulphate, as sodium sulphate, 4·8 mg. per litre was added.

Radiochemical Technique

This was based on the methods fully set out by Layton (1949, 1950) and by Kodicek and Loewi (1955-56).

Enough cartilage slices to give a dry weight of about 20 mg. were incubated in 5 ml. medium at 37° C. in a water bath with a shaking machine. The sulphate in the medium was labelled with approximately 5 microcurie ^{35}S per ml. (carrier-free sulphate supplied by Radiochemical Centre, Amersham). Duplicate or triplicate assays were made with nearly all specimens. In each experiment a boiled sample of the same cartilage was incubated as a control.

After 4 hours' incubation, the cartilage slices were rinsed with ice-cold isotonic (2·5 per cent.) sodium sulphate and then stored for 24 hrs at 4° C., the sodium sulphate solution being changed four times during this period. The boiled control confirmed the adequacy of this technique to remove unbound labelled sulphate.

The slices were then blotted dry and further dried overnight on watch glasses at 60° C. in a hot-air oven. They were then weighed, fused with anhydrous sodium carbonate in platinum crucibles, and dissolved in *N* HCl. These solutions were transferred to 70-ml. silicone-lined centrifuge tubes, and their volume was adjusted to about 50 ml. with distilled water, and the pH to the yellow colour change of bromophenol blue (about pH 3). The tubes were placed in a 95° C. water bath and 5 ml. 0·05*N* sodium sulphate added as carrier; all the sulphate was then precipitated as barium sulphate by adding 3 ml. *N* barium chloride. After being allowed to crystallize at 95° C. for 2 hrs, the solutions were cooled to room temperature, then centrifuged, and the precipitate washed twice with distilled water and once with 70 per cent. alcohol and filtered through disks of filter paper over a sintered glass funnel to give a uniformly thick deposit of barium sulphate.

A standard of 1 ml. of a 1 : 250 dilution of the radio-activated incubation medium was prepared in the same way at the same time.

The precipitates were counted on the filters, using a thin mica end-window Geiger-Müller tube. All samples were counted for at least 2,000 counts. Counts per minute per mg. dried cartilage were calculated, and by comparison with the standard, the absolute uptake of sulphate was obtained. For convenience this result was expressed as micrograms (μg.) of sulphate per gram (g.) of dried tissue. Actual weights rather than counts allow results to be compared over a period, extreme accuracy in activation of the medium is unnecessary, and no allowance for radioactive decay need be made, provided that a standard of radio-activated medium is used on each occasion. No significant activity was detected in any boiled cartilage control.

Results

Decline in Sulphate Utilization by Stored Cartilage and by Cartilage post mortem

Boström and Månsson (1953), working with calf cartilage, and Curran and Gibson (1955-56), working with human cartilage, have already proved the expectation that the cells of cartilage removed from the body gradually lose their ability to fix sulphate *in vitro*. It was also to be expected that cartilage remaining in the cadaver would show a progressive loss of activity after somatic death, but we know of no quantitative investigations on this point. Our first experiments were therefore designed to give us enough information on *post mortem* and storage decay to enable us to judge the effects of this on our later results.

Storage at 4° C.—All specimens stored in incubation medium at 4° C. showed a decline in ability to fix sulphate when subsequently incubated at 37° C. The absolute values for sulphate uptake in the ten biopsy specimens of costal cartilage are shown in Fig. 1, and, since there was a wide range in the initial amounts of sulphate taken up, the results are expressed as a percentage of the initial activity in Fig. 2. These figures show that the decline is regular in eight of the ten specimens and so slow that 50 per cent. of activity is not lost until the third or fourth day of storage; 21 necropsy specimens of costal cartilage were assayed in the same way at intervals up to 2½-11 days in store at 4° C. The rate of decline was more varied from specimen to specimen. True initial uptakes were unobtainable, since a variable number of hours had elapsed between death and necropsy. There were

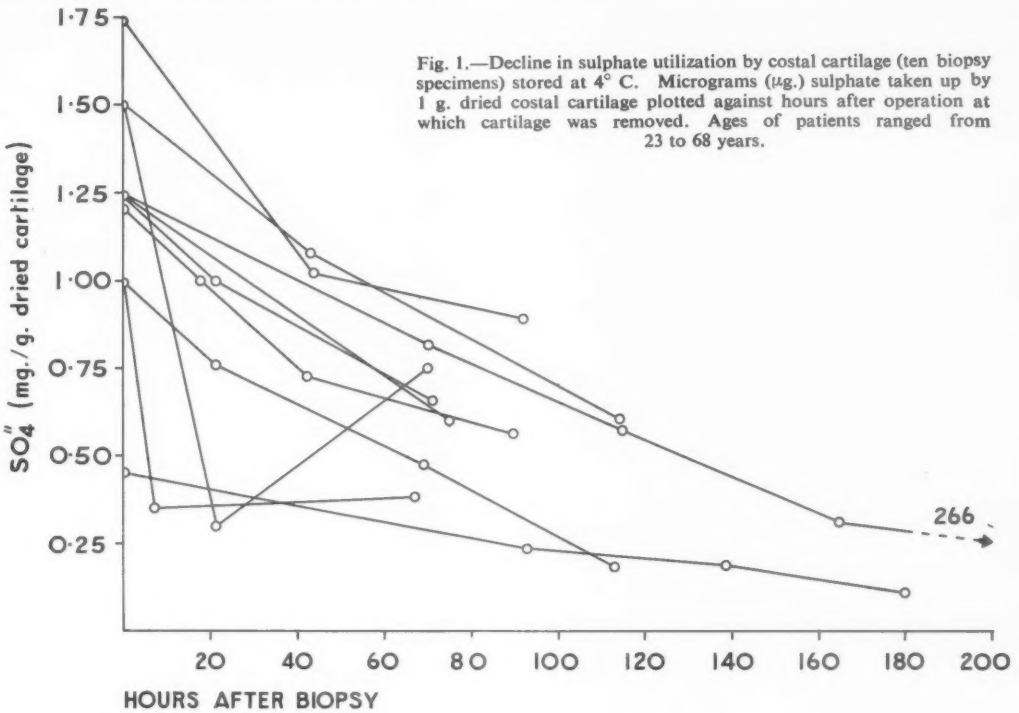

Fig. 1.—Decline in sulphate utilization by costal cartilage (ten biopsy specimens) stored at 4° C. Micrograms (μg.) sulphate taken up by 1 g. dried costal cartilage plotted against hours after operation at which cartilage was removed. Ages of patients ranged from 23 to 68 years.

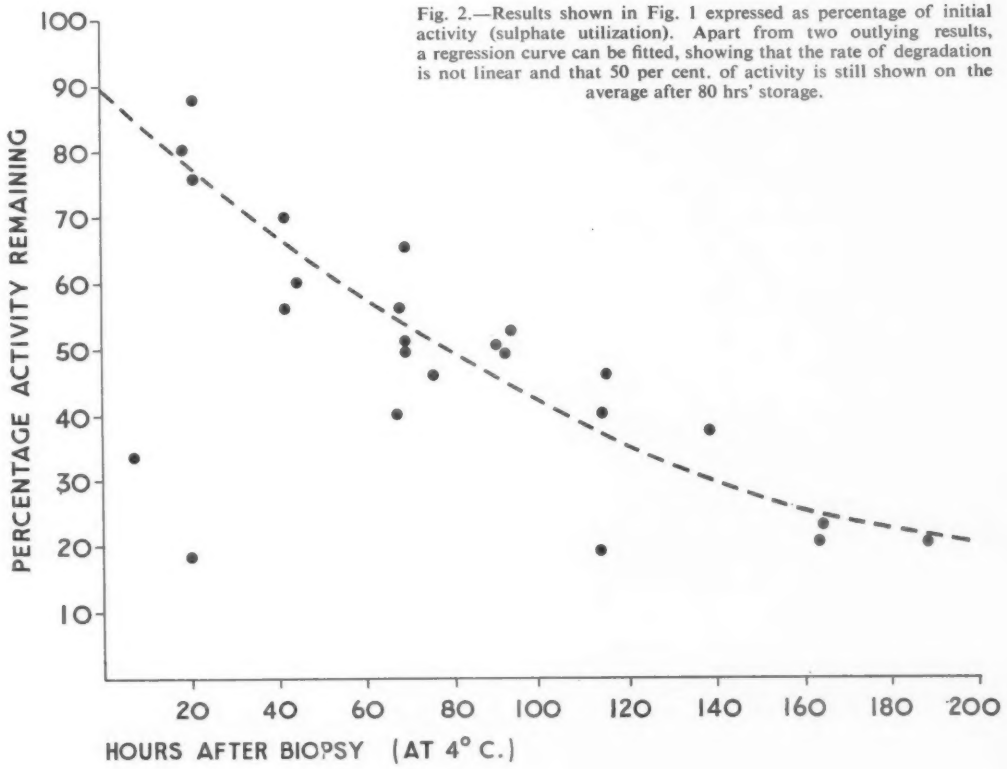

Fig. 2.—Results shown in Fig. 1 expressed as percentage of initial activity (sulphate utilization). Apart from two outlying results, a regression curve can be fitted, showing that the rate of degradation is not linear and that 50 per cent. of activity is still shown on the average after 80 hrs' storage.

more children in the *post mortem* series whose cartilage showed a very high uptake of sulphate (Fig. 3). The general pattern of decline in sulphate-fixing activity resembled that shown by the biopsy material.

Storage at Room Temperature.—Diminished chondrocyte activity in utilizing sulphate developed much more rapidly at room temperature than in the refrigerator. Fig. 3 illustrates this phenomenon in an experiment where assays were made in parallel on cartilage stored in incubation medium at room temperature and at 4° C.

Cleaning of Cartilage.—It was found that the power to fix sulphate was much more rapidly lost by cartilage when the perichondrium and attached fibro-muscular tissues were left attached. We therefore adopted the practice of isolating clean pieces of cartilage with their surfaces scraped free from adventitial tissues as soon as they were removed from the body.

Influence of Age on Chondrocyte Activity in Costal Cartilage

The age of the subject influences the amount of sulphate fixed. This is very obvious when the results from infants are compared with those from older children and adults. The autoradiograph of a section of costal cartilage of an infant (Fig. 4) shows a strikingly different picture from that of an old man's costal cartilage (Fig. 5). The cells are more numerous in the infant cartilage and each gives a more intense image in the overlying emulsion; some of the cells of the aged cartilage show no uptake of radioactive sulphate.

Many senile costal cartilages contained microscopic foci of calcification, themselves evidence of a reduced viability of the chondrocytes (Hass, 1956). These tended to cause variable results to be obtained from different samples of the same cartilage, but all results were in a low range.

There was little delay in handling the ten biopsy samples of costal cartilage, and their uptake of sulphate (range 1·74-0·45 μg. SO_4 per g. dried

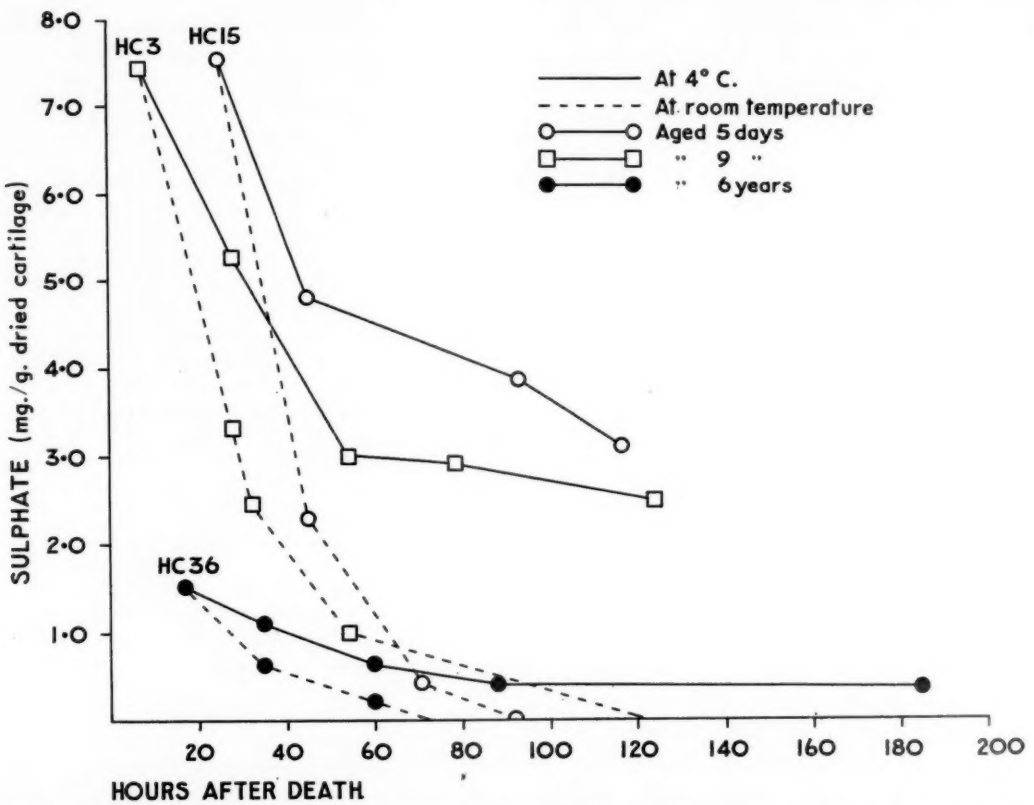

Fig. 3.—Degradation of cartilage obtained *post mortem* when stored at room temperature and at 4° C. Absolute values of sulphate intake plotted against time in hours.

Fig. 4.—Autoradiograph (exposed for 6 weeks) of section of costal cartilage from an infant aged 11 days, obtained 18 hrs after death. Blackening over all chondrocytes shows intense sulphate fixation in a highly cellular field. × 90.

Fig. 5.—Autoradiograph (exposed for 6 weeks) of section of costal cartilage from a man aged 83 years. Cells are sparse and some show no evidence of sulphate fixation. × 90.

cartilage) was generally higher than that of *post mortem* samples, although no children were included in the biopsy group (see Fig. 1).

The results from the 44 *post mortem* samples of costal cartilage are grouped by age of patient in Table I. Sulphate utilization is high in infants a few days old, less high in older children, and much lower in the adult and elderly. When considering these absolute values, allowance must be made for the time elapsing between death and necropsy. The range of these times is shown in the Table, but no correction factor for the individual case can be calculated. The trend towards loss of chondrocyte function with age is, however, clear enough.

TABLE I

COSTAL CARTILAGES OBTAINED *POST MORTEM*, BY AGE OF PATIENT

Chondrocyte activity expressed as μg. sulphate taken up by 1 g. dried cartilage

Age Group	Number of Cases	Hours after Death		Chondrocyte Activity (μg. SO_4'' per g. dried costal cartilage)	
		Mean	Range	Mean	Range
5 days	1	25	—	7·5	—
9 days	1	7	—	7·36	—
11 days	1	18	—	6·63	—
1–11 mths	3	18	9–26	3·88	3·55–4·77
1–15 yrs	4	27	4–53	1·04	0·28–1·75
16–30 yrs	2	20	13–27	0·35	0·27–0·44
31–45 yrs	2	8	7–9	0·55	0·14–0·97
46–60 yrs	11	15	6–28	0·38	0·11–0·64
61–75 yrs	17	14	6–28	0·34	0·10–0·78
76+	2	10·5	10–11	0·29	0·22–0·36

Influence of Age on Chondrocyte Activity in Articular Cartilage

Increasing age did not play the expected role of adversely affecting the uptake of sulphate. On the contrary, chondrocyte activity was unexpectedly high in many elderly subjects. Table II sets out the results obtained from the patellar cartilage in 32 necropsies. No infants were included in this series and each age group shows a considerable range both of quantitative results and of time elapsing between death and necropsy. A comparison of autoradiographs of sections of articular cartilage from a boy of 14 (Fig. 6) and of an old man (Fig. 7) illustrates how active viable chondrocytes persist in the joints though not in the ribs of the elderly.

Osteo-arthritic changes, ranging from superficial flaking to deep fibrillation and even denudation of

TABLE II

ARTICULAR CARTILAGES (PATELLA) OBTAINED *POST MORTEM*, BY AGE OF PATIENT

Chondrocyte activity expressed as μg. SO_4'' taken up by 1 g. dried cartilage

Age Group (yrs)	Number of Cases	Hours after Death		Chondrocyte Activity (μg. SO_4'' per g. dried articular cartilage)	
		Mean	Range	Mean	Range
1–15	2	20	4–36	0·15	0·13–0·17
16–30	2	15	13–17	0·56	0·44–0·68
31–45	3	8	7–9	0·36	0·12–0·67
46–60	7	14	4–30	1·20	0·33–2·61
61–75	16	14	4–27	0·64	0·14–1·53
76+	2	14	11–17	1·25	0·79–1·72

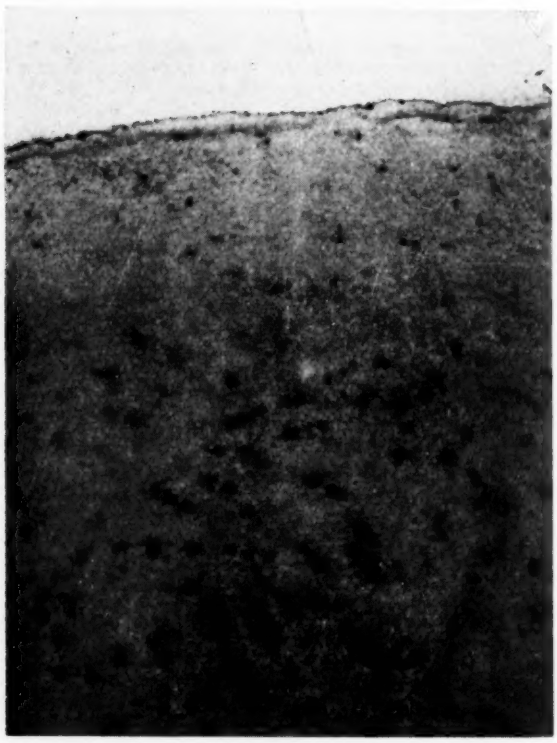

Fig. 6.—Autoradiograph (exposed for 6 weeks) of articular cartilage from a boy aged 14 years, obtained 4 hrs after accidental death. Many active chondrocytes are seen in the mid-zone of the cartilage, but the total estimated activity was not high. × 90.

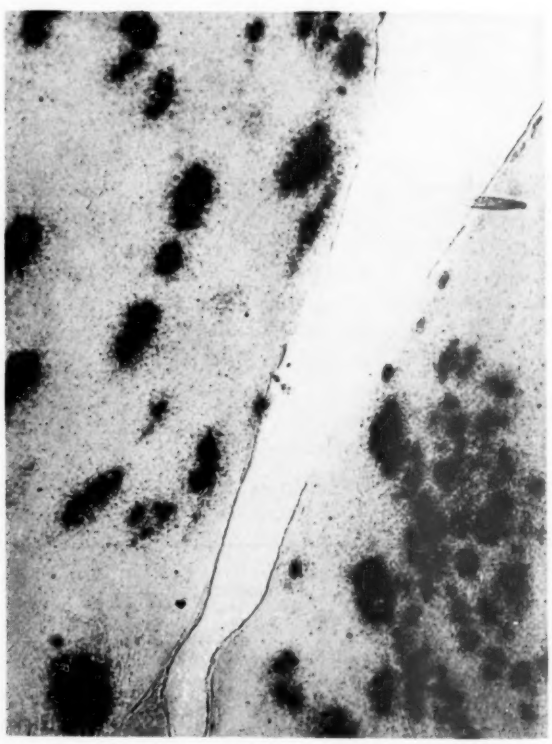

Fig. 7.—Autoradiograph (exposed for 6 weeks) of articular cartilage from a man aged 83 years (same case as Fig. 5). High sulphate utilization by clumps of chondrocytes. × 90.

bone, were present in many patellae. There is a possible relationship between the enhanced sulphate utilization of ageing articular cartilage, the degree of osteo-arthritis, and the peculiar rearrangement and grouping of chondrocytes that are seen in the conventional histological section of the osteo-arthritic cartilage. This is at present being studied and a large number of autoradiographs are in course of preparation. Our analysis of this investigation will be published in due course.

Chondrocyte Activity in Costal and Articular Cartilage compared in a Series of Individuals

The sulphate uptake *in vitro* of costal and articular cartilage were assayed in parallel in 31 cases *post mortem*. These cases are arranged in order of age of patient in Table III.

The trends towards loss of chondrocyte activity with age in costal cartilage (Table I) and towards increased cellular activity in the joints with age (Table II) led to the expectation that the results in the two tissues would diverge in older patients. That this is the case is shown in Table III and in the summarized Table IV, where it is apparent that a considerably greater activity of articular over costal cartilage develops after middle age. No patellar cartilage after this age (44-45 yrs) was free from some degree of cartilage "degeneration". Of the four cases in which the cartilage was intact only one showed greater activity of articular than of costal cartilage. This was case J1 (Table III), a patient

TABLE IV

SUMMARY OF TABLE III BY AGE GROUPS, SHOWING INCREASE WITH AGE OF THE ARTICULAR : COSTAL CARTILAGE ACTIVITY INDEX

Age Group (yrs)	Number of Cases in Each Group	Mean Articular : Costal Cartilage Activity Index
1-15	2	0·15
16-30	2	1·59
31-45	3	2·10
46-60	7	4·64
61-75	15	2·46
76+	2	4·98

TABLE III

31 *POST MORTEM* CASES IN ORDER OF AGE, SHOWING CHONDROCYTE ACTIVITY (EXPRESSED AS μg. OF SO_4'' TAKEN UP BY 1 g. OF DRIED CARTILAGE) OF ARTICULAR AND COSTAL CARTILAGE AND ALSO THE ARTICULAR TO COSTAL CARTILAGE ACTIVITY INDEX

Specimen No.	Age of Patient (yrs)	Time after Death (hrs)	Grade Osteo-arthritis	Chondrocyte Activity (μg. SO_4'' per g. of dried cartilage)		Articular : Costal Cartilage Activity Index
				Articular	Costal	
J 15	4	36	O	0·13	0·62	0·21
J 9	14	4	O	0·17	1·75	0·097
J 25	20	27	I	0·44	0·27	1·63
J 14	30	13	I	0·68	0·44	1·54
J 1	31	8	O	0·12	0·11	1·10
J 24	35	7	O	0·29	0·97	0·30
J 4	44	9	II	0·67	0·14	4·80
J 5	46	6	II	0·35	0·44	0·80
J 17	46	10	II	2·61	0·32	8·20
J 2	50	6	II	1·26	0·11	11·50
J 19	52	11	I	0·33	0·26	1·27
J 12	55	4	I	0·98	0·39	2·50
J 6	58	28	I	0·98	0·25	3·90
J 29	59	30	II	1·89	0·44	4·30
J 10	62	20	I	0·89	0·72	1·23
J 13	65	10	II	0·48	0·20	2·40
J 26	68	11	II	1·14	0·73	1·56
J 8	68	27	IV	0·49	0·13	3·78
J 34	69	21	III	0·90	0·43	2·10
J 22	70	14	I	0·23	0·22	1·04
J 21	71	14	I	0·16	0·19	0·84
J 16	72	14	I	0·14	0·25	0·56
J 31	73	4	III	1·53	0·63	2·43
J 27	73	21	IV	0·78	0·10	7·80
J 7	73	8	II	0·88	0·21	4·09
J 28	74	10	I	0·65	0·26	2·50
J 3	74	8	I	1·0	0·26	3·84
J 32	75	24	II	0·49	0·37	1·33
J 23	75	10	I	0·30	0·21	1·43
J 20	81	17	IV	0·79	0·36	2·16
J 18	83	11	IV	1·72	0·22	7·80

Grades of osteo-arthritic cartilage changes as judged by the naked eye are according to Collins (1949, p. 76).
Grade O: Normal cartilage.
Grade I: Superficial flaking in areas of pressure and movement.
Grade II: More extensive cartilage destruction not denuding bone.
Grade III: Total loss of cartilage in one or more pressure areas and obvious osteophytes.
Grade IV: Complete loss of cartilage from large areas with eburnation of exposed bone; obvious osteophytes.

with a blood dyscrasia treated with cortisone. Cortisone is known to inhibit the fixation of sulphate by cartilage (Layton, 1951; Boström and Odeblad, 1953), but we do not know if this might affect one cartilage area more than another.

We believe that the presence of osteo-arthritis, or age-changes of the same pattern but of less degree, is responsible for the enhanced uptake of sulphate by the cells of the articular cartilage of older subjects, and, indeed, this increase of cellular activity is itself an age-change. Apart from the presence or absence of naked-eye abnormality of the cartilage, the degree of that abnormality, judged on the grades proposed by Collins (1949), does not seem from Table III to be closely related in individual cases with the numerical index of articular : costal cartilage activity, though, when averaged, cartilage changes of Grade I have a lesser mean activity than those of higher grades (Table V).

TABLE V

SUMMARY OF TABLE III BY GRADE OF OSTEO-ARTHRITIS, SHOWING THE HIGHER ARTICULAR : COSTAL CARTILAGE ACTIVITY INDEX WITH VISIBLE CARTILAGE CHANGES

Grade of Osteo-Arthritis	Number of Cases in Each Group	Mean Articular : Costal Cartilage Activity Index
O	4	0·67
I	12	1·84
II	9	4·33
III	2	2·27
IV	4	5·39

Discussion

Layton (1949), using radioactive (^{35}S) sulphate, found by direct measurement after chemical extraction that cartilage takes up the sulphate ion *in vitro*. It is now well established that sulphate is fixed by cartilage in the elaboration of chondroitin sulphate *in vitro* as well as *in vivo* (Boström, 1952; Boström and Månsson, 1953; Boyd and Neuman, 1954). Furthermore, Pelc and Glücksmann (1955) and Curran and Gibson (1955-56), using autoradiographs, have demonstrated that the uptake of sulphate is a function of the intact chondrocyte, and Curran and Gibson clearly state that this may be used as a test for the viability of the cell.

The ability of animal cartilage to incorporate sulphate is reduced by homogenization before incubation, by freezing and thawing, by heating to a temperature over 43° C., by incubating in an atmosphere of nitrogen, by cyanide, malonate, mersalyl, cortisone, and many other substances (Boström and Månsson, 1953; Boyd and Neuman, 1954; Curran and Gibson, 1955-56). In the present study we found that cartilage in fluid medium brought momentarily to the boil loses all ability to fix sulphate. Sulphate uptake increases with rising temperature up to 43° C. (Boström and Månsson, 1953), and when glucose is added to this medium (Boyd and Neuman, 1954). All this information leads to the conclusion that the uptake of sulphate by cartilage is a vital cellular process and one that is involved in chondroitin-sulphate synthesis. Hence it can be concluded that by measuring sulphate utilization we are measuring the rate of synthesis of chondroitin-sulphate in a sample of cartilage by the cells it contains.

Most quantitative measurements of the amount of sulphate fixed by cartilage have been carried out in animals. The ability of calf cartilage to fix sulphate decreases with increasing length of time after slaughter, and after 4 days only little activity remains (Boström and Månsson, 1953). Increasing age has also been shown to influence adversely this function of the chondrocyte (Layton, 1951; Boström and Månsson, 1953; Dziewiatkowski, 1954). Embryonic chick cartilage was found to be 200 times more active than adult cartilage (Boyd and Neuman, 1954). Qualitative studies with autoradiographs have previously shown that human costal cartilage remains viable for up to 72 hrs in the cadaver (Gibson and Curran, 1957). The present study confirms this quantitatively by showing that measurable amounts of sulphate are fixed by samples of cartilage obtained at routine *post mortem* examinations made at intervals up to 36 hrs after death. The initial assays on *post mortem* cartilage, when compared with the higher counts obtained from biopsy samples, suggest that cartilage deteriorates more rapidly in the cadaver than when stored *in vitro*. This is not due only to the slower cooling of the whole body but, in our view, is largely accounted for by the retention of perichondrial tissues. Curran and Gibson (1955-56) noted that cartilage stored in plasma clot showed a more rapid loss of vitality.

The uptake of sulphate may be taken as a measurement of chondrocyte respiration, and is inhibited by anything that inhibits cell respiration (Boyd and Neuman, 1954). The results of studies with ^{35}S are, in general, well in line with the observations by Bywaters (1937) on the respiration of cartilage. Bywaters studied glycolysis in cartilage; oxygen consumption was generally too little for direct measurement. He pointed out that respiratory estimations must take into account not only the weight of the tissue investigated but its cell population; foetal rabbit cartilage showed ten times as much glycolysis per mg. but only twice as much per cell. The very high sulphate uptake by infant rib cartilage in our cases is certainly due in some measure to its

great cellularity, but autoradiographs (Fig. 4) also suggest a more intense radioactivity over each cell.

Not all cartilage cells in a tissue slice show uniform activity. Curran and Kennedy (1955) demonstrated by injections of labelled sulphate into mice *in vivo*, that the mature chondrocyte shows the greatest utilization of sulphate; the least mature cells adjoining the perichondrium and the large vacuolated cells towards the centre do not retain the ion to the same extent. Dziewiatkowski (1951) also showed in the rat epiphysis that newly differentiating and post-mature cartilage cells used relatively little sulphate. These considerations imposed certain precautionary steps on us in sampling our specimens. Every costal cartilage from which results are here included was sliced in full transverse section so that our assay results express the activity of all the chondrocyte population of the specimen.

Despite these precautions, the interpretation of findings in the investigation of costal cartilage is not easy. Øwre (1936) stated that degeneration took place so early and was of such general occurrence in rib cartilage that he was unable to draw conclusions from his observations in regard to any constitutional tendency to cartilage degeneration. In our study the frequency of microscopic foci of degeneration and calcification and their irregular distribution made results difficult to interpret. However, certain trends were noticeable. On storage at 4° C., there is a steady decline in activity (Figs 1 and 2). The regularity of decline was most obvious in biopsy material, and this decline was greatly accelerated at room temperature (Fig. 3). These results are in agreement with the behaviour of animal tissues already described (Boström and Månsson, 1953). Table I shows that chondrocyte activity in costal cartilage falls rapidly in early childhood and probably continues to fall through adolescence, but the fall in later adult life is not statistically significant. What is important is that the activity does not seem to rise again as does the activity of articular cartilage (Tables II and IV).

The differing metabolism of human costal and articular cartilage, more pronounced with increasing age, is the main matter that we have demonstrated in the present investigation. This disposes of the view that a generalized or systemic degradation occurs in all the cartilage cells of the body as age advances. We have never assumed that all cartilage throughout the body might have the same metabolic activity. Mouse autoradiographs (Pelc and Glücksmann, 1955) have shown that such is not the case. But the change with ageing in the articular : costal cartilage activity index has not previously been measured in any species.

It remains to discuss the relationships between the increased activity of chondrocytes with age, and osteo-arthritic fibrillation and destruction of cartilage (Tables III and V). Matthews (1952) showed that the content of chondroitin sulphate was greater and that of collagen less in weight-bearing than in non-weight-bearing cartilage. In a later paper, however, Matthews (1953) showed that there was a relative loss of chondroitin sulphate in the fibrillated areas of osteo-arthritic cartilage. Chrisman, Bechtol, Coelho, Rose, and Brennan (1958) discovered elevations of inorganic sulphate in joint fluid in established degenerative arthritis, and advanced the theory that degenerating cartilage might be the source of this sulphate. Is it the case that not only is sulphate liberated by disintegrating matrix, but that the articular cartilage cells are overactive in synthesizing more sulphated compound?

Summary and Conclusions

The utilization, or fixation, of labelled sulphate ion, $^{35}SO_4$, is a measure of chondroitin-sulphate synthesis by cartilage cells.

This function of the chondrocytes has been studied *in vitro* in 54 samples of human costal cartilage and in 32 samples of articular (patellar) cartilage. Ten biopsy samples of costal cartilage were obtained at operation; in all other cases the material was collected at necropsy.

The results of radiochemical assay have been expressed as μg. sulphate taken up by 1 g. dried cartilage. Autoradiographs have also been prepared, and consideration has been given to matters of cell population and the viability of individual cells.

Storage of cartilage in incubation medium at 4° C. leads to a slow decline in chondrocyte function, but 50 per cent. of activity still remains after 3 to 4 days (Figs 1 and 2). Chondrocyte activity declines more rapidly when cartilage is stored at room temperature (Fig. 3) and when the perichondrial tissues are left *in situ*.

In costal cartilage, sulphate utilization is high in infants a few days old, less high in older children, and much lower in the adult and elderly (Table I). This is due to the increased cellularity and to more active individual cells in young cartilage (Figs 4 and 5).

In articular cartilage, by contrast, sulphate utilization tends to increase as age advances (Table II, Figs 6 and 7).

Parallel studies of costal and articular cartilage were made *post mortem* in 31 cases, the time after death and the storage conditions being the same for the two samples. In young subjects costal

cartilage is more active than articular, but after middle age, and especially when "degenerative" changes are present in the joint, there is considerably greater activity of articular over costal cartilage (Tables III, IV, and V).

The evidence presented disposes of the view that there may be a general or systemic degradation of cartilage cell function throughout the body as age advances. It shows, moreover, that, even in severe "degenerative" (osteo-) arthritis, the chondrocytes have not lost their ability to synthesise chondroitin sulphate; indeed this function seems to be stimulated.

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Comparaison de la fonction des chondrocytes des cartilages articulaire et costal humains par la mesure de l'absorption *in vitro* de sulfate marqué (^{35}S)

RÉSUMÉ

L'utilisation, ou fixation, de l'ion sulfate marqué $^{35}SO^4$ permet de mesurer la synthèse de chondroïtin-sulfate par les cellules cartilagineuses.

Cette fonction des chondrocytes fut étudiée *in vitro* sur 54 prélèvements de cartilage costal et 32 de cartilage articulaire (rotulien). Dix prélèvements de cartilage costal furent effectués en chirurgie; dans tous les autres cas le matériel fut obtenu en autopsie.

Les résultats des analyses radio-chimiques est exprimé en μg. de sulfate fixé par 1 g. de cartilage sec. On obtint aussi des autoradiographies et on prit en considération la population cellulaire ainsi que la viabilité des cellules individuelles.

La conservation du tissu cartilagineux en un milieu d'incubation à 4° C. mène à une lente diminution de la fonction chondrocytaire, de manière qu'elle descend à 50% au bout de 3 à 4 jours (figs 1 et 2). L'activité chondrocytaire baisse plus rapidement en température ambiente (fig. 3) at lorsqu'on laisse *in situ* les tissus périchondriaux.

Dans le cartilage costal, l'utilisation du sulfate est élevée chez des enfants âgés de quelques jours, moindre chez des enfants plus grands et très basse chez des adultes et des personnes âgées (Table I). Cela est dû à un contenu supérieur en cellules et une plus grande activité cellulaire dans le cartilage jeun (figs 4 et 5).

Dans le cartilage articulaire, par contre, l'utilisation du sulfate tend à augmenter avec l'âge (Table III, figs 6 et 7).

Des études parallèles sur le cartilage costal et articulaire furent effectuées *post mortem* en 31 cas, le temps depuis la mort et les conditions de conservation étant les mêmes pour les deux types d'échantillon. On observa que chez des sujets jeunes le cartilage costal est plus actif que l'articulaire, mais, après l'âge moyen, surtout en présence d'altérations articulaires "dégénératives", c'est le cartilage articulaire qui est plus actif (Tables III, IV et V).

Les données présentées ci-dessus détruisent l'hypothèse selon laquelle il y aurait une diminution générale et systématique de la fonction des cellules cartilagineuses dans l'organisme entier au fur et à mesure que l'âge avance. Elles montrent aussi, que même dans de sévères (ostéo-) arthrites "dégénératives", les chondrocytes ne perdent par leur capacité de former le chondroïtin-sulfate; tout au contraire, cette fonction semble être stimulée.

Comparación de la función de los condrocitos de los cartilagos articular y costal humanos, utilizando la medida de la absorción *in vitro* de sulfato marcado (^{35}S)

SUMARIO

La utilización, o fijación, del ión sulfato marcado $^{35}SO^4$ es una medida de la síntesis del condroitin-sulfato por las células cartilaginosas.

Esta función de los condrocitos fué estudiada *in vitro* en 54 muestras de cartílago costal y 32 de cartílago articular (rotuliano). Diez de las muestras de cartílago costal fueron tomadas biópsicamente durante intervenciones; en todos los demás casos el material fué obtenido en necropsias.

El resultado de los análisis radio-químicos se expresa en μg. de sulfato fijado por 1 g. de cartílago seco. Igualmente se obtuvieron autoradiografías, y se tomó en consideración la población celular así como la viabilidad de las células individuales.

La conservación del tejido cartilaginoso en un medio de incubación a 4° C. lleva a una lenta disminución de la función de los condrocitos, pero después de 3 o 4 días aún queda un 50% de esta actividad (figs 1 y 2). La

actividad de los condrocitos baja más rápidamente en la temperatura ambiente (fig. 3) y cuando se deja *in situ* los tejidos pericondriales.

En el cartílago costal, la utilización del sulfato es elevada en los niños de pocos días de edad, menor en los niños mayores y mucho más baja en los adultos y ancianos (Tabla I). Esto es debido a un superior contenido en células y a una mayor actividad celular en el cartílago joven (figs 4 y 5).

En el cartílago articular, por el contrario, la utilización del sulfato tiende a incrementarse con la edad (Tabla III, figs 6 y 7).

Estudios paralelos en cartílago articular y costal fueron realizados *post mortem* en 31 casos, siendo idénticos el tiempo transcurrido desde la muerte y las condiciones de conservación para ambos tipos de muestras. Se pudo apreciar que en los sujetos jóvenes el cartílago costal es más activo que el articular, pero, pasada la edad media, y especialmente cuando existen cambios "degenerativos" en la articulación, el cartílago articular presenta una considerable mayor actividad que el costal (Tablas III, IV y V).

Los datos presentados destruyen la idea de que una disminución general y sistemática de la función de las células cartilaginosas de todo el organismo pueda ocurrir a medida que la edad avanza. Ellos demuestran además que, aun en severas (ósteo-) artritis "degenerativas", la capacidad de los condrocitos de sintetizar condroitin-sulfato no se pierde; al contrario—esta función se ve estimulada.

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USE AND INTERPRETATION OF THE ANTISTREPTOLYSIN TEST

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Numerous laboratory tests have been devised and used with varying enthusiasm as aids in the diagnosis of rheumatic fever, but the establishment of the intimate relationship between this condition and upper respiratory tract streptococcal infection has directed interest mainly to the demonstration of serological evidence of streptococcal activity in rheumatic subjects. Of the various tests used for this purpose, the antistreptolysin "O", originally introduced by Todd (1932a, b), has emerged as the most reliable and consistent, but as yet there is no general agreement as to its true value, possibly due to lack of understanding of its interpretation and limitations.

In this laboratory the estimation of antistreptolysin "O" titres (A.S.L.T.) was undertaken, in the first place, as part of a study on rheumatic heart disease in conjunction with the late area cardiologist, Dr. J. W. Brown. However, it rapidly became established in the area as a routine test in the investigation of acute rheumatism and other diverse clinical conditions.

The experience gained from the interpretations of over 4,000 titrations performed during the past 9 years is summarized below.

Material

The subjects were drawn from general hospitals, from the Hull Rheumatic Unit, and from private practice. There were 363 cases of acute rheumatism, 114 of acute nephritis, and 315 others, making a total of 792 (Table I).

Methods

The method described by Hodge and Swift (1933) was used with the following minor modifications:

(1) A locally isolated strain of group A type 1 beta-haemolytic streptococcus was used in preference to the classical Richards strain as it was a better lysin producer.
(2) Culture medium: Todd-Hewitt's broth as modified by Hodge and Swift (1933).
(3) All dilutions were carried out in isotonic buffered saline as recommended by Herbert and Todd (1941).
(4) The following simplified serum dilution range was adopted: 50, 100, 200, 300, 400, 600, 800, 1,200, 1,600, 2,400.
(5) Red cell suspension: a 2·5 per cent. suspension prepared from pooled human blood obtained from the remains of the normal erythrocyte sedimentation rate samples was found convenient and satisfactory. The anticoagulant used was 3·8 per cent. sodium citrate.

TABLE I

SOURCES OF 792 CASES

Sources of Cases		General Hospitals	Rheumatic Unit, Kingston General Hospital, Hull	General Practitioners	Total
Condition	Acute rheumatism	203	117	43	363
	Acute nephritis	75	28	11	114
	Flitting joint pains	31	8	14	53
	Acute pericarditis	14	9	2	25
	Subacute bacterial endocarditis	10	11	0	21
	Mitral stenosis	45	114	18	177
	Haemolytic streptococcal infections	39	0	0	39
	Total	417	287	88	792

(6) Standard antistreptolysin, supplied by the Standard Serum Laboratories, Carshalton, was used throughout for the titration and standardization of the lysin.

(7) The antistreptolysin titre (A.S.L.T.) was expressed in Todd units, namely the reciprocal of the serum dilution which exactly neutralizes one unit standard lysin.

Results

The results obtained from 792 patients were analysed. In most cases three to four titrations were carried out and in many several titrations were performed over a period of many months. The 275 controls were tested only once.

Controls.—In this, as in all serological tests, what matters most is the controls. For this reason, the sera of 275 normal persons with no known recent streptococcal infection were examined. These controls were drawn mainly from the nursing and other hospital staff including laboratory technicians. Those in the younger age group, however, were mainly traumatic cases and also included other carefully selected hospital patients. The results are shown in Table II.

It will be seen that 88 per cent. gave titres of less than 200 Todd units/ml. and 74 per cent. of 100 or less. The average titre was lower at both extremes of age.

Acute Rheumatism and Acute Nephritis.—The sera of 363 patients with acute rheumatism and 114 with acute nephritis (Ellis, Type 1) were examined. The results are shown in Table III.

It will be seen that the results in both conditions were similar, about 80 per cent. of patients giving titres of 200 Todd units or more. This was virtually a reversal of the result obtained with the controls.

TABLE II

ANTISTREPTOLYSIN TITRE DISTRIBUTION IN 275 HEALTHY CONTROLS

Antistreptolysin Titres (Todd Units)	Percentage Distribution by Age Group (yrs)					
	1–10	11–20	21–40	41–60	Over 60	All Ages
Nil	50	40·9	35·7	46·8	52·8	43·6
100	35·3	27·3	32·2	28·5	30·5	30·6
150	11·8	15·9	16·6	11·7	11·1	13·8
200	2·9	11·4	10·7	7·8	2·8	8·0
Over 200	—	4·5	4·8	5·2	2·8	4·0
Total Controls	34	44	84	77	36	275

TABLE III

ANTISTREPTOLYSIN TITRE DISTRIBUTION IN VARIOUS CLINICAL CONDITIONS

Condition		All Cases	Percentage Reactors in each Group		
			Reactors		Non-Reactors
			High Titre (Over 400 units/ml.)	Low Titre (200–400 units/ml.)	Titre (Under 200 units/ml.)
Acute Rheumatism	Over 10 years Old	308	47·3	36·2	16·5
	10 years and Under	55	41·8	36·3	21·8
Acute Nephritis	Over 10 years Old	74	39·2	35·2	25·6
	10 years and Under	40	52·5	25	22·5
Flitting Joint Pains		53	35·8	22·7	41·5
Acute Pericarditis		25	28	28	44
Subacute Bacterial Endocarditis		21	4·8	19	76·3
Mitral Stenosis		177	3·4	25·5	71·1
Active Haemolytic Streptococcal Infections		39	35·9	43·6	20·5
Total		792			

In both diseases titres of 800 to 1,200 units were commonly found, and two cases of acute nephritis and one of acute rheumatism showed the very high titre of 10,000 units/ml. No statistically significant difference was found between the results in children and in adults, but few children were examined.

Other Illnesses (Table III and Fig. 1).—In 39 cases of known streptococcal infection (mainly puerperal pyrexia and scarlet fever) where haemolytic streptococci (group A with very few group C or G) had been isolated, a similar pattern of distribution of reactivity was found.

In 53 cases of "flitting joint pains" and in 25 cases of acute pericarditis about 50 per cent. were reactors.

177 cases of mitral stenosis and 21 cases of subacute bacterial endocarditis showed a similar pattern, with a low percentage of positives consisting mainly of low reactors.

Fig. 1 compares the A.S.L.T.s in the normal controls with those in persons with various diseases.

Antistreptolysin Response in Rheumatic Fever

The A.S.L.T. in patients with rheumatic fever usually shows a special pattern with an initial lag and a slow rise to a maximum in 5 to 6 weeks (after the initial sore throat), slowly tapering off over a period of several weeks. Cases with complications (*e.g.* carditis or relapse) show a striking see-saw pattern (Coburn, 1936; Rothbard, Watson, Swift, and Wilson, 1948).

The drop of the antistreptolysin titre almost always lags behind that of the erythrocyte sedimentation rate and in many cases the A.S.L.T. continues to rise while the E.S.R. is falling.

Case Notes

Fig. 2 (opposite) shows a typical sequence of events in an uncomplicated "monocyclic" case of rheumatic fever, in a girl aged 7 years with a history of joint pains and pyrexia of 4 to 5 days' duration when first seen by her doctor. She had complained of sore throat 3 weeks before the onset of joint pains. Her response to salicylate therapy was excellent and she made an uneventful recovery.

Fig. 3 (opposite) shows a typical course in a case of rheumatic fever of the relapsing or "polycyclic" type, in a girl aged 11 years, who had her first relapse during her initial stay in hospital. She was kept under observation as an out-patient for a considerable time, mainly because of

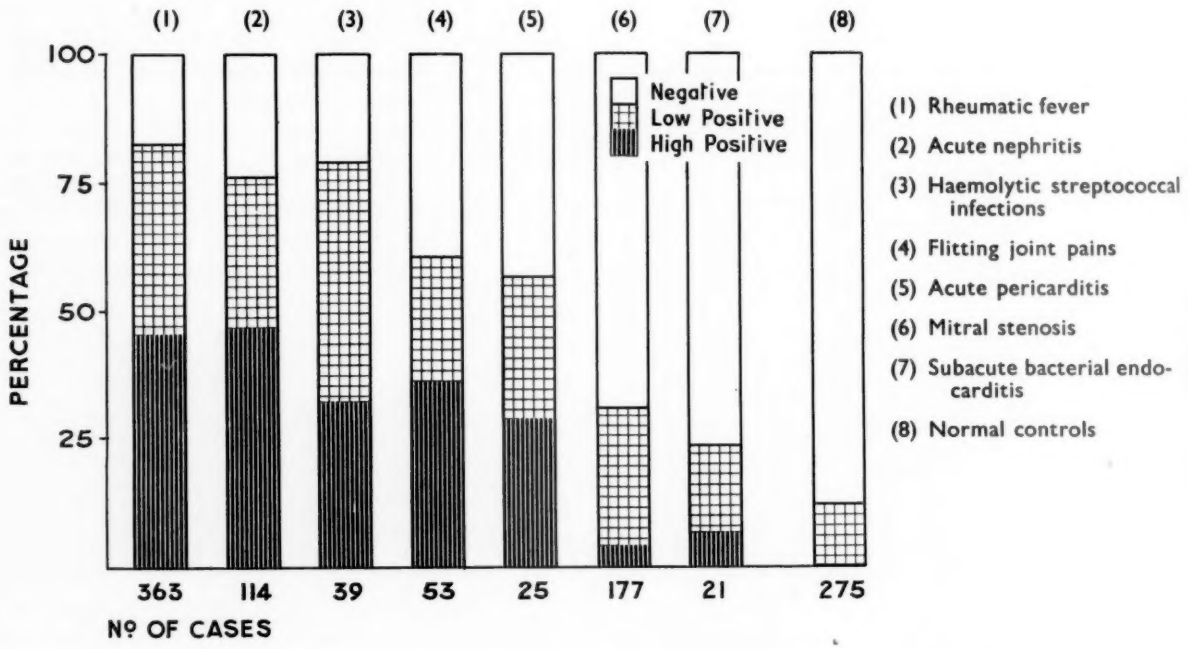

Fig. 1.—Antistreptolysin titres in normal controls (one titration) and in patients with various diseases (three titrations or more).

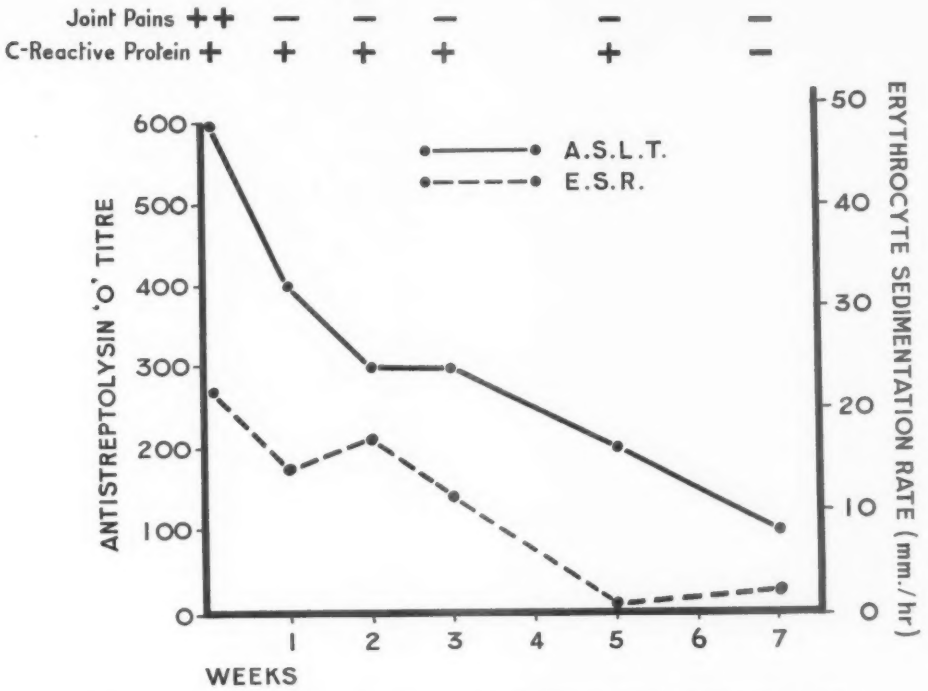

Fig. 2.—Antistreptolysin titre pattern in an attack of rheumatic fever with no complications.

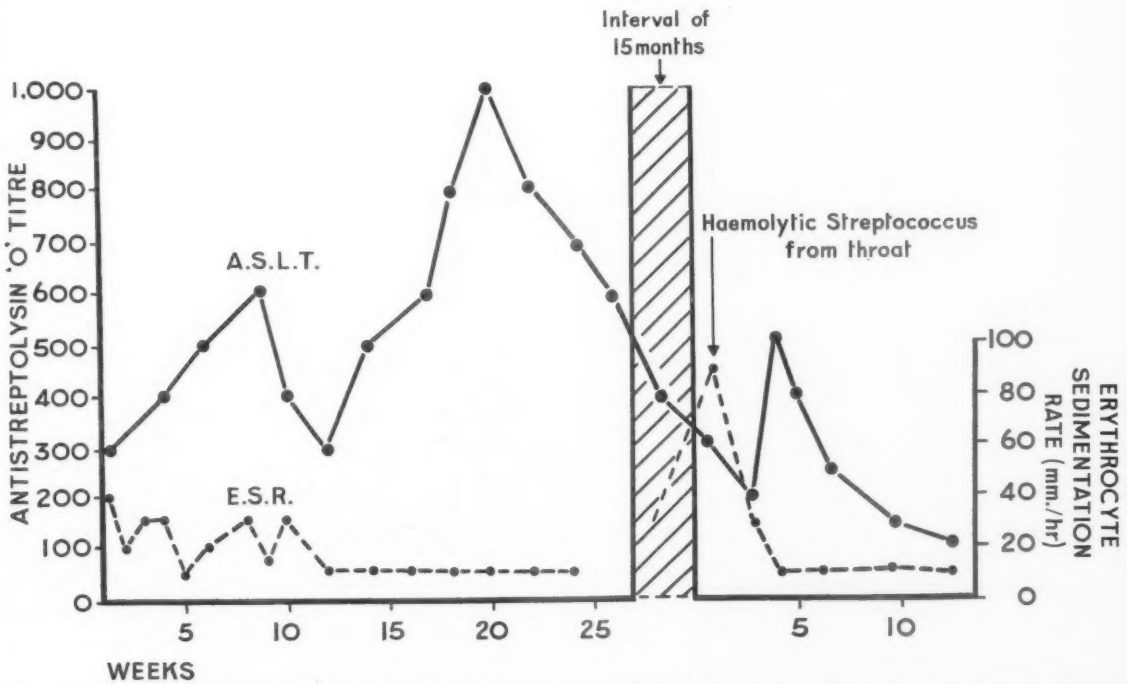

Fig. 3.—Case of rheumatic fever showing typical accelerated massive antistreptolysin titre response during an initial relapse and depressed response following the administration of penicillin during a second relapse.

the persistent elevation of the antistreptolysin titre, and was eventually re-admitted 15 months later with sore throat, joint pains, and active carditis. On this occasion a haemolytic streptococcus was isolated from the throat, and she was treated with penicillin.

Discussion

To interpret the results of the test, it is essential to know the normal antistreptolysin level. Whilst most workers agree that 200 Todd units/ml. or above is abnormal (Rantz, Randall, and Rantz, 1948; Rantz, 1955), many have considered this figure or even 250 units as the upper limit of normality (Wood and McCarty, 1954; Hollinger, 1953).

The results of the present survey support the former view. The fact that about 12 per cent. of the normal population sampled showed a titre of 200 and over is probably due to the presence of subclinical streptococcal infection of the upper respiratory tract.

Nevertheless, the difficulty of defining the demarcation line between normal and abnormal must be regarded as one of the limitations of the test. It is therefore necessary to seek evidence of a significant rise or fall in titre in all cases, especially those with initial low levels. The most that can be said about a single finding of a high titre is that it provides supportive evidence in clinically established cases.

Another limitation of the test is the fact that only 80 to 85 per cent. of cases of clinically established rheumatic fever and acute nephritis will show a significant antistreptolysin response (Table II); even in cases of active streptococcal infection 20 per cent. of the subjects failed to develop this antibody. This, however, need not detract from the value of the test if the following points are borne in mind:

(1) The A.S.L.T. is not a test for rheumatic fever or acute nephritis, but a test for evidence of activity of Lancefield's Group A streptococci (or occasionally Groups C and G). As such, the intensity of the response necessarily varies with the duration of activity of the stimulus. Therefore the duration of the antecedent sore throat, the type of treatment then administered, and a history of previous attacks are important factors. While serological evidence may be detected during the second week after the infection, the maximum response does not generally develop before 5 or 6 weeks and may be partially suppressed by antibiotic therapy (Kilbourne and Loge, 1948). On the other hand, during a relapse, the titre rises much more quickly and to higher levels.

(2) Different strains of Group A streptococci vary greatly in their antigenic capacity (Lancefield and Stuart, 1944; Herbert and Todd, 1944).

(3) The antibody response mechanism in certain individuals is sluggish (Wilson and Miles, 1955).

It should also be recalled that Group A streptococci produce an extraordinary variety of extracellular substances, several of which (including streptolysin, hyaluronidase, and streptokinase) stimulate the production of readily measurable antibodies. Some investigators, by testing for a sufficient number of these antibodies, have been able to demonstrate that approximately 100 per cent. of their rheumatic fever cases show unequivocal response to at least one of these streptococcal components (Rothbard and others, 1948).

These other tests, however, are difficult to perform and to standardize, and remain as yet in the domain of pure research, while the antistreptolysin has proved accurate and reliable and appears to be the one likely to yield most information if its limitations are well understood.

It is therefore important to emphasize the following points:

(1) No matter what the initial A.S.L.T. may be, the demonstration of a rise in titre should be sought in all cases with initial low levels. At least two to three repeated titrations at not less than 1-week intervals may be necessary to establish the presence or absence of a significant response. A four-fold or two-tube rise in a straight doubling dilution is accepted as significant.

(2) Although the absence of a rise in titre does not necessarily exclude recent streptococcal infection, a persistent titre of 50 or less is almost certain evidence against rheumatic fever or acute glomerulo-nephritis, and such a result at least merits a critical re-assessment of the clinical diagnosis (Wood and McCarty, 1954). On the other hand, the failure of the A.S.L.T. to show a significant drop during late convalescence from acute rheumatism strongly indicates continued streptococcal activity and with it the possibility of relapse.

The antistreptolysin test can be of help to the clinician in a variety of conditions such as "flitting joint pains", where the diagnosis is notoriously difficult or in cases of acute pericarditis where frequently no evidence of rheumatic aetiology is obtained, although only about 50 per cent. of them show a significant titre.

In mitral stenosis and sub-acute bacterial endocarditis the percentage of positive reactors is quite low as would be expected on clinical grounds. However, these include the occasional case in which the establishment or exclusion of rheumatic activity is very important.

In a limited series of cases of mitral stenosis, about one-third showed Aschoff's bodies and correlated

closely with a positive A.S.L.T. finding (Brown, 1958). There is also some evidence that patients with high-titre antibodies are more prone to develop the post-valvotomy syndrome (Din, 1958); some clinicians in this area now consider a raised A.S.L.T. sufficient evidence of incipient carditis to delay valvotomy until it subsides.

Summary

(1) An analysis of the results of over 4,000 antistreptolysin titrations (792 cases) is given. Significant titres (200 units/ml. or more) were obtained in 80 to 85 per cent. of cases of acute rheumatism, acute nephritis, and proved haemolytic streptococcal infections.

(2) The limitations of the test arise from the difficulty of defining normal and abnormal antistreptolysin levels and from the failure of some patients to react. These points are discussed.

(3) The importance is stressed of repeating titrations in order to establish a significant serological response.

(4) The usefulness of the test in conditions other than acute rheumatism is discussed.

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Application et interpretation de la réaction a l'antistreptolysine

RÉSUMÉ

(1) On présente une analyse des résultats de plus de 4000 déterminations de antistreptolysine (792 cas). Des titres significatifs (200 unités par c.c. ou plus) furent obtenus dans 80 à 85 pour cent des cas de rhumatisme aigu, nephrite aiguë et dans des cas d'infection confirmée par le streptocoque hémolytique.

(2) Les limitations de la réaction viennent de la difficulté de définir les taux normaux et pathologiques de l'antistreptolysine et du fait que certains malades n'y réagissent pas. On discute ces points.

(3) On souligne l'importance des dosages répétés pour obtenir des réponses sérologiques significatives.

(4) On discute l'utilité de la réaction dans des maladies distinctes du rhumatisme aigu.

Uso e interpretación del test de la antiestreptolisina

SUMARIO

(1) Se da un análisis de los resultados de más de 4,000 determinaciones de antistreptolisina (792 casos). Títulos significativos (200 unidades por c.c. o más) fueron obtenidos en el 80 al 85 por ciento de los casos de reumatismo agudo, nefritis aguda y en casos comprobados de infección por estreptococo hemolítico.

(2) Las limitaciones del test nacen de la dificultad de definir los niveles normal y patológico de antistreptolisina y del fallo de ciertos enfermos en reaccionar. Son discutidos estos puntos.

(3) Se insiste sobre la importancia de repetir las titulaciones en orden a establecer una respuesta serológica significativa.

(4) Se discute la utilidad de la prueba en enfermedades distintas al reumatismo agudo.

Ann. rheum. Dis. (1959), **19**, 48.

PRODUCTION OF LUPUS ERYTHEMATOSUS (L.E.) CELLS IN THE DOG BY THE TRANSFUSION OF SYSTEMIC LUPUS ERYTHEMATOSUS PLASMA

BY

GEORGE BENCZE

WITH THE TECHNICAL ASSISTANCE OF

MARY LUDÁNYI

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(Director: Prof. M. Julesz)

The production of the lupus erythematosus cell phenomenon by the transfusion of lupus erythematosus plasma in three patients with malignant disease was the subject of an earlier report (Bencze, Cserhati, Kovacs, and Tiboldi, 1958). Numerous unsuccessful attempts have been made to produce L.E. cells in animals. The present paper reports the results of systemic lupus erythematosus (S.L.E.) plasma transfusion in six dogs, a seventh dog being used as a control.

Method

Plasma was obtained under sterile conditions from three patients with systemic lupus erythematosus (S.L.E.), in whose peripheral blood L.E. cells could be repeatedly demonstrated by the rotatory method of Zinkham and Conley (1956), using 10 ml. citrate to 100 ml. blood. The blood obtained in this way was kept for 24 hrs at 4° C., centrifuged for 15 min. at 6,000 r.p.m., and incubated at 37° C. for 30 min. before use.

Each dog received a drip-transfusion of 4 to 5 ml./kg. body weight. Plasma from Donor 1 (K.E.) was given to Dogs 1 and 2, from Donor 2 (O.P.) to Dogs 3 and 4, and from Donor 3 (T.J.) to Dogs 5 and 6. The sixth dog received 50 ml. S.L.E. plasma and 50 ml. normal control plasma, and Dog 7 (Control) received normal plasma only (Table).

L.E. cells were looked for in the peripheral blood of the dogs before and immediately after the transfusion and at 30 minutes and 1, 2, 4, 6, 24 and 48 hrs after the transfusion, by the method of Zinkham and Conley (1956).

Results

Experiment 1.—90 ml. plasma obtained from Donor 1 (K.E.) was transfused into Dog 1 and 60 ml. into Dog 2. The transfusion was uneventful. A few L.E. cells could be found in the peripheral blood of Dog 1 for 6 hrs and in Dog 2 for 2 days (Figs 1 and 2, opposite).

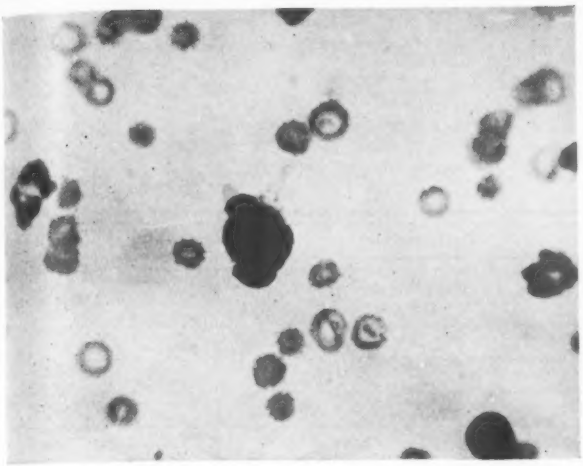
Experiment 2.—60 ml. plasma obtained from Donor 2 (O.P.) was transfused into Dogs 3 and 4. The transfusion was uneventful. Only a few L.E. cells could be detected after 1 and 2 hrs, but the number then increased and reached the maximum 6 hrs after the transfusion, when 50 to 60 L.E. cells per 1,000 leucocytes were present in Dog 4 as compared with 30 to 40 in the donor (Fig. 3, opposite).

Experiment 3.—Dog 5 received 90 ml. and Dog 6 50 ml. plasma from Donor 3 (T.J.). The transfusion was uneventful. No L.E. cells could be detected immediately after the transfusion but a few were seen after 30 min. The maximum number was seen in each dog within 4 to 6 hrs of the transfusion, 50 to 60 L.E. cells per 1,000 leucocytes being present as compared with 30 to 40 in the donor. The number of L.E. cells had fallen 24 hrs after the transfusion, but some were still present after 6 days in Dog 5 and after 9 days in Dog 6 (Figs 4 and 5, opposite).

Experiment 4.—Normal human plasma obtained in a similar way was used in a control test.

50 ml. normal plasma was given to Dog 6 24 days after the transfusion of S.L.E. plasma. During this second transfusion the animal developed nausea and vomiting and experienced a state of shock. Adrenaline was administered subcutaneously and intracardially, and its condition improved after 90 minutes.

The method of Zinkham and Conley (1956) showed no L.E. cells either immediately after



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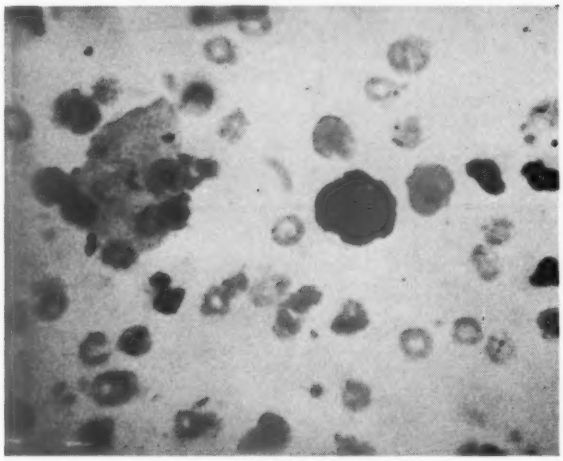

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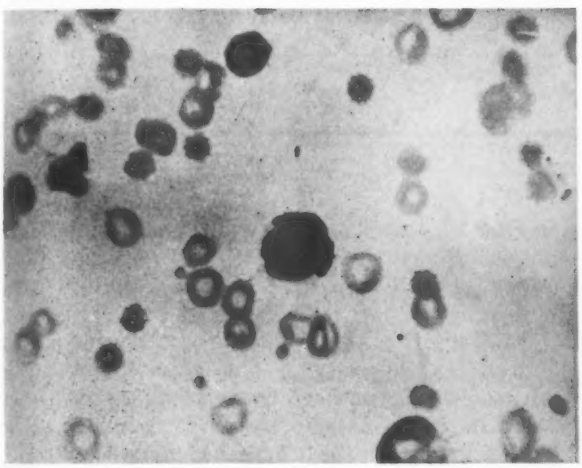

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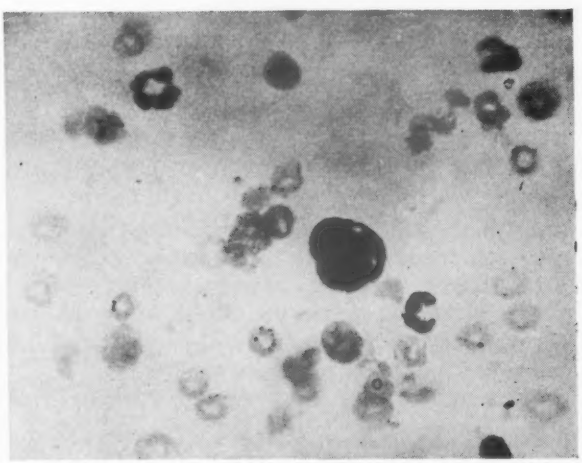

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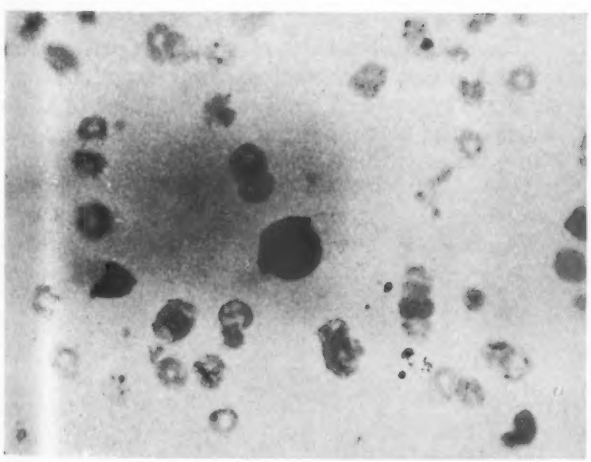

(5)

Fig. 1.—L.E. cell in peripheral blood of Dog 1, 60 min. after plasma transfusion.

Fig. 2.—L.E. cell in peripheral blood of Dog 2, 2 hrs after plasma transfusion.

Fig. 3.—L.E. cell in peripheral blood of Dog 4, 6 hrs after plasma transfusion.

Fig. 4.—L.E. cell in peripheral blood of Dog 5, 6 days after plasma transfusion.

Fig. 5.—L.E. cell in peripheral blood of Dog 6, 9 days after plasma transfusion

Experiment No.	Dog No.			S.L.E. Donor	Recipient Dog			Donor Plasma	
					Sex	Body Weight (kg.)	Blood Group	ml.	Blood Group
1	Same Donor	1		K.E.	♀	18	AB	90	O
		2		K.E.	♂	12	AB	60	O
2	Same Donor	3		O.P	♀	13	B	60	A
		4		O.P	♂	12	E	60	A
3	Same Donor	5		T.J.	♀	21	B	90	A
		6	Same Recipient	T.J.	♂	10	AB	50	A
4				Normal Plasma (Control)	♂	10	AB	50	A
		7		Normal Plasma (Control)	♂	23	B	90	A

transfusion, or 30, 60, or 120 min. later. Two hours after the transfusion the dog died suddenly, probably through bleeding due to the cardiac puncture.

No untoward response followed the normal plasma transfusion in Dog 7, and the results of L.E. cell examinations were negative.

The results of the four experiments are summarized in the Table.

Discussion

Transfusion experiments were carried out on six dogs with plasma obtained from three S.L.E. patients and a seventh dog was used as a control. After the plasma transfusion L.E. cells were found in all six dogs. The maximum was reached within 4 to 6 hours, when the number of L.E. cells in Dogs 4, 5, and 6 surpassed that in the blood of the donors. After 24 hrs the number of L.E. cells decreased. In Dog 1 L.E. cells were present for 6 hrs, in Dog 2 for 48 hrs, and in the others for 3, 6, and 9 days respectively. Feulgen L.E. cells reactions were positive.

As a control normal plasma was given to Dogs 6 and 7. Dog 6, who had previously received S.L.E. plasma, developed severe shock and died 2 hrs later. L.E. cells were not found at all in Dogs 6 and 7 after the injection of normal plasma.

Summary

When L.E. cell positive plasma from patients with systemic lupus erythematosus was transfused into six dogs, typical L.E. cells were observed in all six animals, the maximum number of cells being seen 4 to 6 hrs after the transfusion.

OF LUPUS ERYTHEMATOSUS PLASMA

	L.E. Cells in Recipients													
Transfusion	Time after Transfusion													
	1 min.	30 min.	60 min.	2 hrs	4 hrs	6 hrs	24 hrs	2 days	3 days	4 days	6 days	7 days	9 days	10 days
0	+	+	+	++	++	+	0	0	0	0	0	0	0	0
0	+	+	+	+	+	+	+	+	0	0	0	0	0	0
0	+	+	++	++	++	+++	++	+	+	0	0	0	0	0
0	+	+	+	+++	+++	++++	++	++	+	0	0	0	0	0
0	0	+	++	+	++++	++++	++	++	+	+	+	0	0	0
0	0	+	+++	++++	++++	++++	+++	++	++	++	+	+	+	0
0	0	0	0	0*										
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

* Succumbed 2 hours after transfusion.

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Production des cellules de lupus érythémateux (L.E.) chez le chien par transfusion du plasma des malades atteints de lupus érythémateux disséminé

RÉSUMÉ

Des transfusions du plasma des malades atteints de lupus érythémateux disséminé et contenant des cellules L.E. à six chiens, furent apparaître chez tous les six animaux des cellules L.E. typiques, atteignant un maximum entre la 4-ème et la 6-ème heure après la transfusion.

Producción de células de lupus eritematoso (L.E.) en el perro por transfusión de plasma de enfermos con lupus eritematoso diseminado

SUMARIO

Transfusiones de plasma con células L.E. de enfermos con lupus eritematoso diseminado, a seis perros, resultaron en la presencia de células L.E. típicas en todos los animales, la mayoría de ellas evidenciada entre la cuarta y la sexta hora después de la transfusión.

Ann. rheum. Dis. (1960), **19**, 52.

2,4,6-TRIHYDROXYBENZOIC ACID IN THE TREATMENT OF RHEUMATIC FEVER

BY

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Clarke, Clarke, and Mosher (1958) have recently reported on the therapeutic action of 2,3,6- and 2,4,6-trihydroxybenzoic acid (THB) in twelve patients with rheumatic fever and eleven others. The latter compound, usually in a dosage of 1 to 1·33 g./24 hrs, was believed to have a clinical anti-rheumatic potency six to eight times that of salicylic acid and no toxicity.

We have found it to have no anti-rheumatic potency in classical rheumatic fever, judged by pain and temperature response in three patients receiving doses varying from 1 to 8 g./24 hrs, whereas calcium aspirin (Disprin) in a dosage of about 4 g./24 hrs was dramatically effective in the same three patients (Figure).

REFERENCE

Clarke, N. E., Clarke, C. N., and Mosher, R E. (1958). *Amer. J med. Sci.*, **235**, 7.

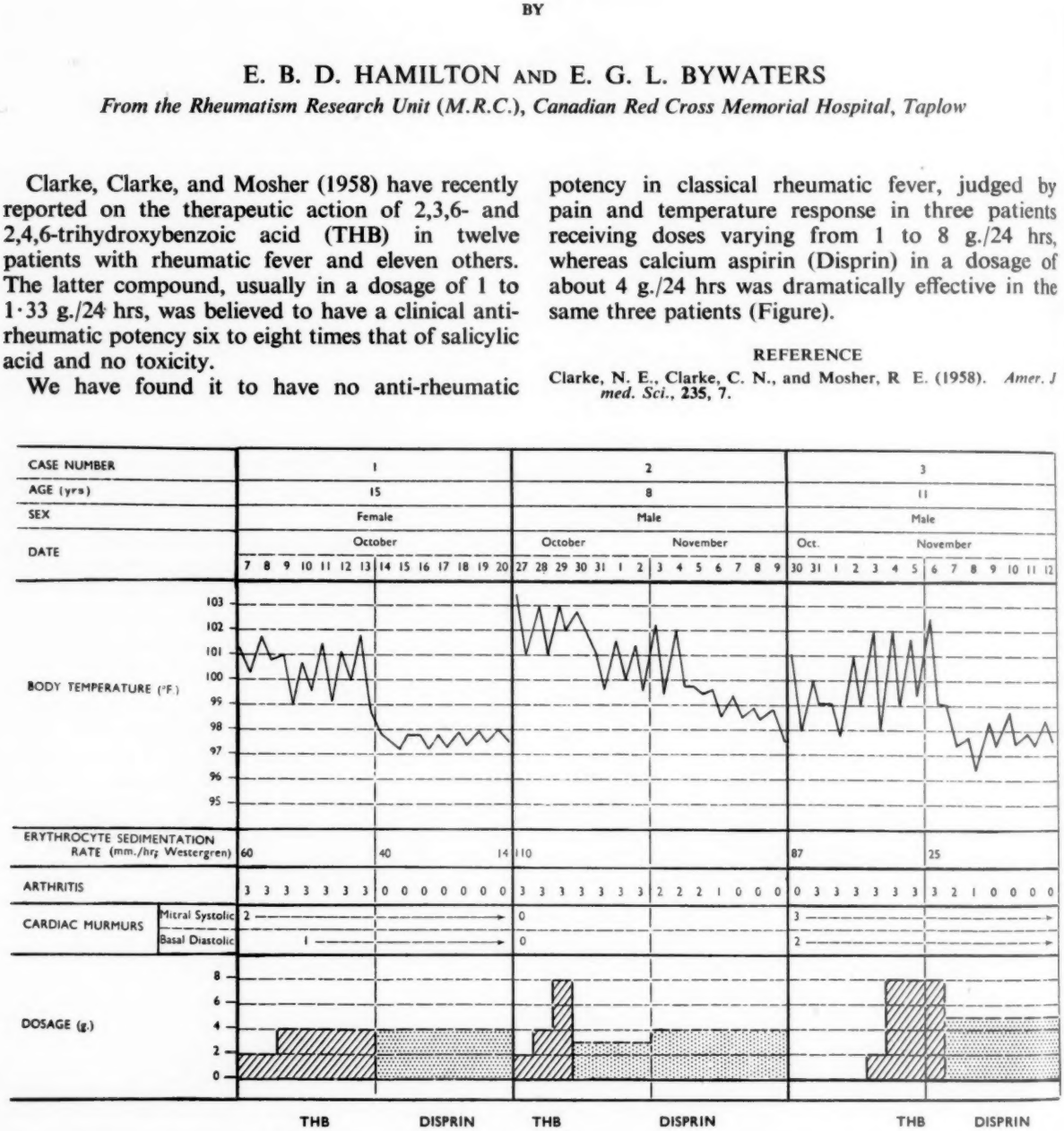

Figure.—Response of fever, erythrocyte sedimentation rate (Westergren), arthritis, and cardiac murmurs in three patients with rheumatic fever, treated with THB and Disprin.

APPENDIX

Case Reports

Case 1, a girl aged 15 years, was admitted to hospital on October 7, 1958, having had a sore throat one month before admission which was followed 10 days later by the onset of flitting polyarthralgia. There had been transient substernal pain for 3 days.

Examination.—The body temperature was 101° F. She had arthritis of the right wrist and left ankle, and an apical pansystolic murmur.

Therapy.—She was started on trihydroxybenzoic acid on October 8, and received 2 g. daily for 2 days and 4 g. daily for 4 days. Throughout this time she ran a high fever with acutely inflamed joints. A soft basal diastolic murmur was first noted on October 10. Both cardiac murmurs were later confirmed by phonocardiogram and an electrocardiogram showed a prolonged PR interval. Because there was no response to THB she was given Disprin 4 g. daily from October 13. There was a prompt fall in body temperature, the joints were normal the following day, and the patient has since made uninterrupted progress.

Case 2, a boy aged 8 years, was admitted to hospital on October 27, 1958, having had a sore throat one month before admission and polyarthralgia for 4 days.

Examination.—The body temperature was 103° F. He had acute arthritis of both wrists and ankles, but no cardiac murmurs.

Therapy.—He was started immediately on trihydroxybenzoic 2 g. daily and this dose was doubled daily for 2 more days, but the treatment was changed to Disprin 3 g. daily on October 30 as he still had acute joint involvement and was running a high fever. The following day the arthritis in the ankles had subsided but there was still slight swelling of the wrists and the body temperature had fallen only slightly. He continued febrile and on November 1 complained of chest pain but no pericardial friction was heard. On November 3 a chest *x* ray showed a large cardiac shadow suggestive of pericarditis but the electrocardiogram was normal. The dosage of Disprin was increased to 4 g. daily, and he continued to improve. On November 8 and 9 the temperature did not rise above 99° F., and the slight swelling of both wrists was less, and he could move them without pain.

Case 3, a boy aged 11 years, was admitted to hospital on October 30, 1958, with a 3-day history of polyarthralgia following a sore throat. This was a second attack of rheumatic fever.

Examination.—A basal diastolic murmur and mitral diastolic murmur were heard in addition to the pre-existing mitral systolic murmur. He had erythema marginatum. The body temperature was 101° F.

Therapy.—Despite being given trihydroxybenzoic acid 2 g. on November 3 and 8 g. daily from November 4 to 6, he remained febrile with pain in the knees and elbows, and marked swelling of the left wrist. When Disprin 5·4 g. daily was started on the evening of November 6, the fever immediately fell to 95° F. and the arthritis subsided.

L'acide 2,4,6-trihydroxybenzoïque dans le traitement du rhumatisme articulaire aigu

RÉSUMÉ

L'acide 2,4,6-trihydroxybenzoïque (THB), à une dose de 1 à 8 grammes par jour, n'eut aucun effet antirhumatismal, jugé par la douleur et la température, sur trois cas de rhumatisme articulaire aigu classique, tandis que l'aspirine calcique (Disprin) administrée aux mêmes malades à la dose de 4 grammes par jour produisit un effet dramatique.

Acido 2,4,6-trihidroxibenzoico en el tratamiento del reumatismo poliarticular agudo

SUMARIO

El ácido trihidroxibenzoico (THB), en dosis diaria de 1 a 8 gramos, no tuvo acción antirreumática alguna, juzgada por el dolor y la temperatura, en tres casos clásicos de reumatismo poliarticular agudo, mientras que la aspirina cálcica (Disprin) administrada a los mismos enfermos en dosis de 4 gramos diarios, produjo un efecto dramático.

Ann. rheum. Dis. (1960), **19**, 54.

ERYTHROCYTE SURVIVAL IN RHEUMATOID ARTHRITIS*

BY

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The cause of anaemia in rheumatoid arthritis has not yet been fully elucidated. Several workers have suggested that haemolysis is at least a contributory factor.

Using the Ashby method for erythrocyte survival study, Alexander, Richmond, Roy, and Duthie (1956) found that normal erythrocytes were eliminated more rapidly than usual from the circulation of patients with rheumatoid arthritis, whereas cells from rheumatoid donors survived normally. Similarly, Freireich, Ross, Bayles, Emerson, and Finch (1957) found a normal survival of patients' erythrocytes in normal recipients but in thirteen rheumatoid recipients normal donor cells were eliminated more rapidly than normal, at a rate which ranged from 1·09 to 2·39 per cent. of the cells per day. This destruction was interpreted as being random, and was thought to suggest the presence of an extrinsic defect.

Radioactive chromium is an isotope which is especially suitable for the study of the life span of erythrocytes, as a patient's cells can be labelled, and after re-injection, studied in their natural environment. The ^{51}Cr now available has a high specific activity (10 mC. per mg.) so that a survival study can be carried out using a low and apparently non-toxic concentration of metallic chromium.

There have been very few previous reports of survival studies in rheumatoid arthritis using this method, and results have been equivocal (Ebaugh, Peterson, Rodnan, and Bunim, 1955; Weinstein, 1959).

In the present paper we describe the results of cell survival studies using ^{51}Cr in fifty patients suffering from rheumatoid arthritis.

Methods

Erythrocyte Survival.—The patients' erythrocytes were labelled with ^{51}Cr by a standard method (Mollison and Veall, 1955) and then re-injected. Venous blood samples were collected 10 to 15 minutes after the injection and subsequently at regular intervals.

Radioactivity of 3-ml. volumes was measured in a well-type scintillation counter with a thallium-activated sodium iodide crystal of 5 cm. diameter. The measurements of the initial blood samples were taken to represent 100 per cent. radioactivity content of the blood, and by comparison with the radioactivity of subsequent samples of blood the rate of loss of radioactivity from the circulation was calculated. Results were corrected for isotope decay and plotted on arithmetic graph paper.

Occult Blood.—Gastro-intestinal blood loss was estimated by measuring the radioactivity of the stools following the labelling process described above. The stools were collected in waxed cartons of 16 oz. capacity, each carton containing a 24-hour collection. The radioactivity was counted by positioning the carton between two scintillation crystals. It was separated from the lower counter by a plastic ring so that the specimen contained in the carton was approximately equidistant from both crystals. The counting system was surrounded by lead shielding and the responses of both crystals counted together. A standard was prepared from 3 ml. venous blood placed in a similar carton and diluted with approximately 100 ml. water. It was assumed that the radiation-absorbing properties of faeces and water are the same, so that the blood content of the faeces could be calculated directly from the ratio of the two counts. This system of counting was found to have a satisfactory geometry and sensitivity.

Routine Haematological Investigations.—Blood counts and other haematological investigations were carried out using standard methods. The erythrocyte sedimentation rate (E.S.R.) was determined by the Westergren method.

Patients.—Investigations were carried out on sixteen men and 34 women who had definite rheumatoid arthritis according to the revised classification of the American Rheumatism Association (Ropes, 1959). In all the patients the disease was active. In 44 the E.S.R. was 15 mm./hr or more, and in the remainder the disease

* Paper presented at a meeting of the Heberden Society on December 5, 1959.

was judged to be active on clinical findings. Ages ranged from 12 to 79 years. Patients with evidence of complicating factors, such as Felty's syndrome or lupus erythematosus, were excluded.

Many of the patients had received various forms of therapy in the past, and salicylates were administered to all during the course of the present investigation. Nine patients were receiving steroids at the time of the commencement of the erythrocyte survival study.

Results

Results of the erythrocyte survival studies were plotted on arithmetic graph paper and compared with the results obtained in a similar study of twenty normal healthy men and women subjects (Fig. 1). They have been corrected for decay but not for elution of chromium from intact erythrocytes. Correction formulae are partly empirical, and it appears to be more satisfactory to interpret results by comparing findings in patients with those in normal subjects without applying any correction factors. The normal range shown consists of the mean measurements in the twenty normal subjects, with two standard deviations. All the measurements in the normal subjects fell within this range. In 46 of the patients with rheumatoid arthritis the measurements of ^{51}Cr activity were within the normal range.

The most useful index of erythrocyte elimination is the time taken for half the originally administered chromium to disappear from the circulation ($T\frac{1}{2}^{51}Cr$). The normal range has been reported variously to be between 23 and 40 days (Berlin, Waldmann, and Weissman, 1959). In our normal subjects it was found to be 25 to 35 days.

In 46 of the patients with rheumatoid arthritis, $T\frac{1}{2}^{51}Cr$ was between 25 and 35 days. In the remaining four cases $T\frac{1}{2}^{51}Cr$ was 24, 23, 23, and 19 days, respectively.

As stated above, correction formulae are generally unsatisfactory, but by applying an elution correction it is possible to determine, at least approximately, the pattern of a survival curve and the mean cell life.

In Cases 47 to 50, graphs of erythrocyte survival have been replotted, after correction for an elution half-time of 64 days, as suggested by Hughes Jones and Mollison (1956). The results have been compared with the normal range, similarly corrected (Fig. 2, overleaf).

In these four cases there is an early loss of approximately 15 per cent. of the erythrocytes and thereafter the remaining cells appear to be eliminated at a normal rate, so that the slope of elimination parallels that of the normal subjects. In Cases 48 and 49, survival studies were repeated approximately 6 months later. On this occasion there was no demonstrable early loss of ^{51}Cr, and $T\frac{1}{2}^{51}Cr$ was 35 days and 29 days respectively, with a normal slope of elimination.

During the erythrocyte survival studies all stools were collected and the blood content estimated. The figures in the Table (overleaf) represent the average daily blood loss over a 30-day period. In Case 48, this was 20 ml. per day, and at least theoretically this could account for the increased rate of elimination of ^{51}Cr from the circulation. On the second labelling there was a loss of only 1 ml. per day when the survival study showed a normal rate of elimination. However, in Case 49, there was no such correlation, and 5 ml. per day was the average loss throughout both survival studies. Moreover, the relatively large average amounts of blood lost in

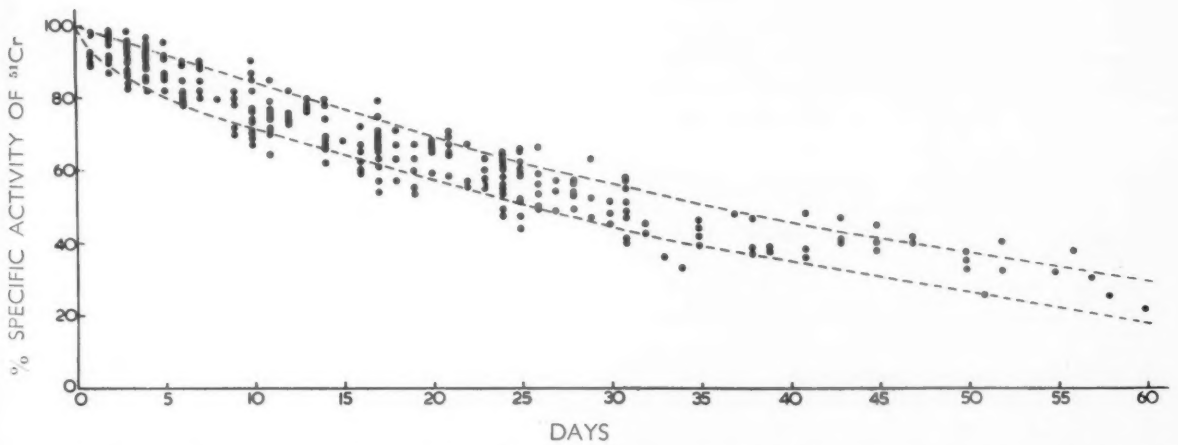

Fig. 1.—Erythrocyte survival studies in fifty patients with rheumatoid arthritis. Results have been corrected for isotope decay but not for chromium elution. The normal range (twenty subjects) is shown by the interrupted lines.

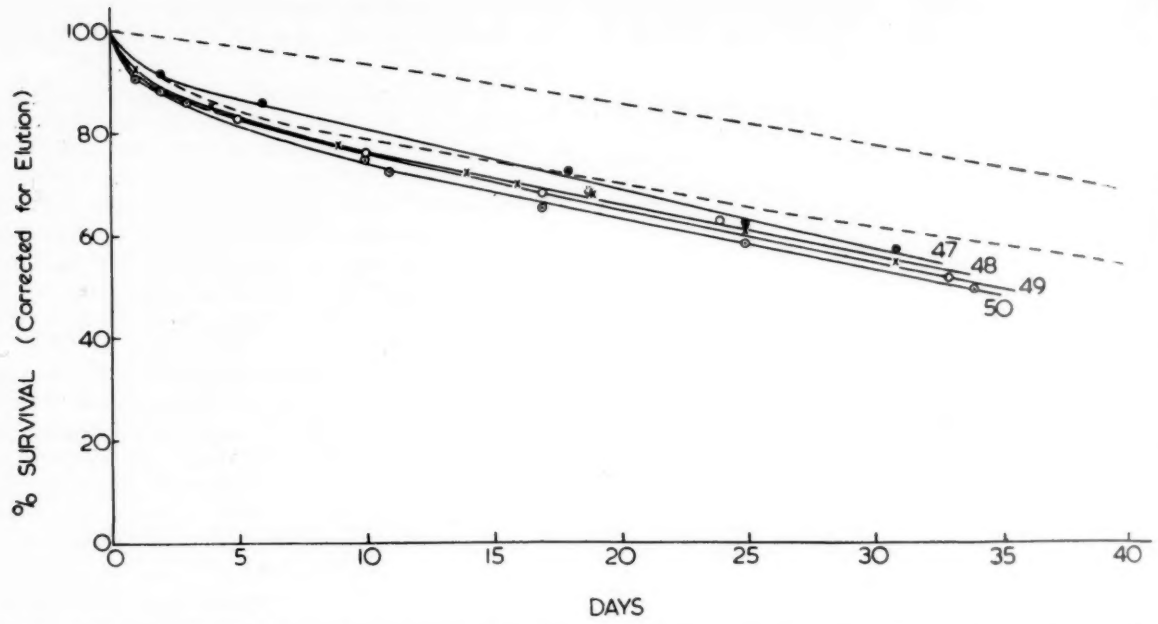

Fig. 2.—Erythrocyte survival studies in four patients in whom the results fell outside the normal range. Corrections have been applied for isotope decay and for elution of chromium.

Cases 17 and 23 were not associated with measurable increased elimination from the circulation. In some cases the daily amount of blood loss varied from nil to 50 ml., but the "early loss" of radioactivity from the circulation in Cases 47, 48, 49, and 50 was not associated with increased gastro-intestinal bleeding during that period.

A number of the patients were anaemic but there was no obvious close relationship between the degree of anaemia and the activity of the disease (Table, opposite).

Discussion

There have been few reports of erythrocyte survival studies in rheumatoid arthritis and the principal previous observations have been made on the results of studies using the Ashby method. However, this technique has limitations; it is now recognized that cross transfusions not infrequently result in diminished survival even when there are no demonstrable antibodies (Mollison, 1959). It is conceivable that the incompatibility may be even greater in patients with rheumatoid arthritis. By the use of radioactive chromium it has been possible to study the survival of the erythrocytes of such patients in their natural environment.

Erythrocyte survival studies have been carried out on fifty patients with active rheumatoid arthritis in a number of whom there have been varying degrees of anaemia.

In 46 of the fifty patients, erythrocyte survival was normal and in only four was there evidence of an increased rate of erythrocyte elimination. This was due to an "early loss" of approximately 15 per cent. of the labelled erythrocytes, with a subsequent normal slope of the curve. The reason for the early loss of radioactivity from the circulation is unexplained, though an early loss of approximately 10 per cent. is often encountered in normal subjects (Mollison, 1959). But even if the "early loss" in the patients with rheumatoid arthritis had been of greater significance than that which occurs in normal subjects, the increased rate of cell elimination is only slightly greater than normal. The early loss was not associated with any concomitant fluctuation in packed cell volume or with excessive blood loss. It was not seen on a subsequent occasion in two of the patients in whom survival studies were repeated under conditions similar to those of the first study.

Gastro-intestinal bleeding occurred to a varying extent in all but one of the patients, but except possibly in one instance (Case 48) the amount was not sufficient to have had a significant influence on the rate of elimination of the labelled erythrocytes from the circulation.

The occurrence of haemolysis in patients with lupus erythematosus and Felty's syndrome is well recognized, and has been demonstrated in several

TABLE

CLINICAL AND HAEMATOLOGICAL DATA AND RESULTS OF ^{51}Cr STUDIES IN FIFTY PATIENTS WITH RHEUMATOID ARTHRITIS

Case No.	Age (yrs)	Sex	Duration of Disease (yrs)	Hb (g./100 ml.)	E.S R. (mm./hr)	$T\frac{1}{2}^{51}Cr$ (days)	Daily Mean Gastro-Intestinal Blood Loss (ml.)
1	49	F	1	11·9	125	35	2
2	54	F	5	11·8	50	35	3
3	55	M	3	12·8	117	34	1
4	61	F	4	11·1	78	34	3
5	25	M	12	15·8	30	33	3
6	63	F	19	12·9	80	33	4
7	55	F	5	11·9	85	33	3
8	51	F	1	14·2	18	31	2
9	63	F	19	11·6	94	31	2
10	48	F	10	11·0	55	31	1
11	34	F	1	10·4	108	31	1
12	60	F	16	11·5	80	30	2
13	65	M	16	11·4	80	30	2
14	78	F	20	11·2	66	30	2
15*	29	F	10	10·9	10	30	1
16†	66	F	14	10·8	69	30	2
17†	50	F	1	8·9	70	29	9
18†	58	F	4	8·1	112	29	3
19†	79	F	6	12·7	63	28	2
20†	39	F	8	12·5	82	28	1
21*†	54	F	2	12·4	28	28	1
22*	51	F	7	11·5	73	28	2
23	65	F	16	10·5	88	28	7
24*	48	M	20	16·0	37	27	3
25	64	F	5	15·2	60	27	1
26*	73	M	16	14·9	15	27	0
27	56	M	15	14·5	10	27	3
28	46	M	2	12·9	39	27	2
29*	49	F	4	12·8	25	27	1
30	40	F	1	10·3	83	27	2
31†	25	M	3	10·2	70	27	1
32†	50	M	1	15·2	5	26	1
33	57	F	5	12·5	60	26	3
34†	61	F	17	12·3	14	26	3
35	52	F	17	11·1	80	26	1
36*	69	M	20	10·8	76	26	1
37	42	F	20	10·6	45	26	1
38	74	F	15	9·1	24	26	1
39†	63	M	5	14·8	30	25	2
40	50	F	25	14·1	31	25	1
41*	69	F	23	13·6	10	25	2
42	67	M	13	13·4	30	25	1
43†	51	F	12	13·2	10	25	2
44	12	M	1	11·8	63	25	5
45†	54	M	4	10·8	90	25	4
46	18	M	10	9·7	56	25	6
47	47	F	13	12·4	68	24	1
48‡	21	F	4	12·4	40	23	20
49‡	53	F	20	13·6	100	23	5
50†	40	M	23	14·3	26	19	3
Normal Range		M		13·5–18·0	3–5	25–35	0
		F		11·5–16·4	4–7	25–35	0

* Patient on steroid therapy before and during survival study.
† D.A.T. less than 16, but diagnosis established by presence of nodules and/or *x*-ray changes.
‡ Survival studies were repeated approximately 6 months later with the following results:

Case No.	Hb (g./100 ml.)	$T\frac{1}{2}^{51}Cr$ (days)	Daily Mean Gastro-Intestinal Blood Loss (ml.)
48	11·9	35	1
49	12·6	29	5

patients investigated by us, but not reported here. The present series did not include any patients with such complicating features.

Several of the patients with normal erythrocyte survival had received steroid therapy before and at the time of the investigation. It is, of course, possible that cell survival was influenced by this treatment, but by far the greatest number of patients with normal survival had not received any treatment other than salicylates.

Summary

Using the isotope ^{51}Cr as a label, erythrocyte survival studies were carried out in fifty patients with active rheumatoid arthritis. In all cases the patient's own cells were labelled.

No cases of Felty's syndrome or lupus erythematosus were included in the series.

In 46 of the patients (92 per cent.), erythrocyte survival was normal. In the remaining four patients, there was only a slight increase in the rate of cell elimination, caused by the early loss of approximately 15 per cent. of the labelled cells. The reason for this "early loss" is unknown. Gastro-intestinal bleeding occurred to a varying extent in almost all of the patients, but in only one case was the amount sufficient to have had a detectable influence on the rate of elimination of the labelled erythrocytes from the circulation.

Haemolysis is not a feature of rheumatoid arthritis, and is not a significant factor in the development of the anaemia which is often associated with the disease.

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Discussion.—DR. W. R. M. ALEXANDER (*Edinburgh*) said that unpublished work by Richmond had confirmed these findings. The thought had occurred to him that, in rheumatoid arthritis, the erythrocytes reaching the peripheral circulation were relatively resistant to destruction, the more susceptible cells being destroyed in the marrow. This might explain the normal elimination of rheumatoid erythrocytes and slightly more rapid elimination of healthy erythrocytes in rheumatoid arthritis.

DR. J. J. R. DUTHIE (*Edinburgh*) said that they should remind themselves that normal cells were undoubtedly destroyed more rapidly when introduced into the rheumatoid circulation. A rheumatoid red cell might develop a resistance to this process.

PROF. J. H. KELLGREN (*Manchester*) said that he understood from the authors' definition that any patient showing presumptive evidence of haemolysis, *e.g.* large spleen, leukopenia, etc., was eliminated from the study, and asked whether that would be a correct estimation?

DR. LEWIS replied that in the few cases in which there was an early loss of a percentage of the radio-activity, this occurred rapidly and appeared to conform to the pattern which is frequently seen in normal subjects, in whom the $T\frac{1}{2}$ of this early loss has been estimated to be $1\frac{1}{2}$ days. In normal subjects it has been thought unlikely that this represents a population of cells especially susceptible to destruction, but rather to some process such as elution of the ^{51}Cr. In any event, this early loss occurred in only four of the patients studied.

With regard to selection of material, the investigation was undertaken in order to assess whether haemolysis occurred in uncomplicated rheumatoid arthritis and whether it could be blamed for the anaemia which may be found even in the absence of complications such as hypersplenism. Several of the patients included in the series were anaemic with haemoglobin values as low as 8 g. per cent. In cases with hypersplenism, haemolysis is well recognized, and had been demonstrated in several patients studied during the course of the present investigation.

Survie des érythrocytes dans l'arthrite rhumatismale

RÉSUMÉ

On étudia la survie des érythrocytes chez cinquante malades atteints d'arthrite rhumatismale évolutive; l'isotope ^{51}Cr fut utilisé pour marquer des globules rouges de chaque malade.

La vie moyenne des érythrocytes fut normale chez 46 malades (92%). Chez les quatre malades restants, le taux d'élimination des globules rouges n'augmenta que très peu; cette augmentation fut causée par une perte initiale de 15 pour cent environ des érythrocytes marqués. On ne connaît pas la raison de cette "perte initiale". Chez presque tous les malades on nota des hémorragies gastrointestinales d'intensité variable, mais dans un cas seulement la perte sanguine fut suffisante pour se refléter dans le taux d'élimination des érythrocytes marqués.

L'hémolyse n'est pas un caractère de l'arthrite rhumatismale et ne constitue pas un facteur appréciable dans l'anémie qui souvent accompagne cette maladie.

Vida media de los eritrocitos en la artritis reumatoide

SUMARIO

Se estudió la vida media de los eritrocitos en cincuenta enfermos con artritis reumatoide evolutiva, sirviéndose del isótopo readioactivo ^{51}Cr para marcar los hematies de cada enfermo.

La vida media de los hematies fué normal en 46 de los enfermos (92%). En los otros cuatro enfermos hubo solamente un ligero aumento en la tasa de eliminación de los eritrocitos, ocasionado por la temprana destrucción de un 15 por ciento aproximadamente de los hematies marcados. La causa de esta "temprana destrucción" es desconocida. En casi todos los enfermos se detectó hemorragia gastrointestinal de grado variable, pero solamente en un caso fué lo suficiente copiosa para reflejarse en la cifra de eliminación de los eritrocitos marcados de la circulación.

La hemolisis no es una característica de la artritis reumatoide, y por tanto no puede ser considerada como un factor significativo en la anemia que con frecuencia aparece en dicha enfermedad.

BOOK REVIEWS

Gouty Arthritis and Gout. By T. E. Weiss and A. Segaloff. 1959. Pp. 221, 58 figs, bibl., index. Thomas, Springfield, Ill.; Blackwell, Oxford. (60*s.*)

To quote from the preface "This compilation of theories, facts, clinical observations, pathology, treatment, and extensive bibliography was undertaken to furnish the student, clinician, and investigator with a usable reference on gout." The text is readable, well illustrated, and up to date. Each chapter can be read on its own, which is useful for reference, although at the cost of appearing somewhat repetitious to the reader who follows the whole text through. The authors' own experience of 280 patients with gout enlivens the chapter on clinical finding and complications. An extensive bibliography (394 references) is well reviewed and covers almost all the relevant literature in the English language. (Only nine references are made to papers in German or French.) There are one or two topics—such as the prevalence of gout and hyperuricaemia—which are not mentioned and there are occasional textual errors (for example "rarer" instead of newer (p. 51, line 6)). But these are minor defects. The authors have stated their object and have achieved it, and in doing so have given us a first-rate book on gout.

A. St. J. Dixon.

Radiodiagnostic en rhumatologie. 400 images de base. By S. de Seze, A. Djian, and M. Phankim-Chapuis. 1960. 188 pp., 400 figs. Expansion Scientifique, Paris. (30 *N.F.*)

This loose-leaf collection of 400 small reproductions of radiographs of diseases of interest in rheumatology is intended for students of the subject and should prove of some value. Most of the illustrations make their point, but reduction in size, and reversal of normal white on black, lack verisimilitude. Advertising matter on every page mars an otherwise good idea and an attractive presentation.

A. St. J. Dixon.

X INTERNATIONAL CONGRESS OF RHEUMATOLOGY

Rome, 1961

The Tenth International Congress of Rheumatology will be held in Rome on September 4 to 7, 1961, under the presidency of Prof. L. Villa.

Those who wish to contribute a paper to the scientific sessions are asked to submit to the Scientific Committee by December 31, 1960, the title and a 200-word summary in triplicate (with an English and French translation). There will be simultaneous translation at the congress into English, French, German, Italian, and Spanish.

All requests for general information should be addressed to the General Secretary of the Congress, Prof. C. B. Ballabio, Clinica Medica Generale, Via F. Sforza 35, Milano, Italy.

For scientific information and particulars of the exhibition of rheumatological literature, please write to Prof. Alessandro Robecchi, Centro di Reumatologia dell'Ospedale San Giovanni Battista, Corso Bramante 88, Torino, Italy.

For information concerning the location of the Congress, the exhibition of scientific material, and accommodation, please write to Prof. Tomaso Lucherini, Istituto di Reumatologia del l'Università IX Padiglione, Policlinico Umberto 1, Rome, Italy.

Ann. rheum. Dis. (1960), **19**, 60.

HEBERDEN SOCIETY

ANNUAL REPORT, 1959

At the Annual General Meeting held on December 5, 1959, Sir Stanley Davidson was unanimously elected an Honorary Member of the Society.

The following new members were elected:

Ordinary Members: Dr. Barbara Ansell, Dr. L. J. Barford, Mr. J. C. F. Cregan, Dr. J. E. Dawson, Dr. G. O. Storey;

Associate Members: Dr. D. A. Brewerton, Dr. N. Cardoe, Dr. H. Coke, Dr. C. E. Quin, Dr. D. G. Scott;

Overseas Members: Dr. J. Baum, Dr. S. K. Banerjee, Dr. J. H. Bland, Dr. D. Nicholson;

Continental (European) Members: Dr. W. Hijmans, Dr. R. Lescure.

The total Ordinary Membership was thus brought up to 98 and the Associate Membership to twenty.

Activities

At the invitation of Dr. W. S. Tegner and Dr. R. M. Mason, the first clinical meeting of the year was held at the London Hospital, February 27, 1959 (*Annals*, **18**, 145). Papers were presented by Dr. R. M. Mason, Dr. R. D. Catterall, Dr. W. G. Wenley, Dr. D. Greenbaum, Dr. V. L. Steinberg, and Mr. O. J. Vaughan-Jackson (all from the London Hospital).

In connexion with the centenary celebrations of the Devonshire Royal Hospital, Buxton, a joint meeting was held with the British Association of Physical Medicine, on July 25, 1959 (*Annals*, **18**, 147, 259). The morning was devoted to the Heberden Society, when papers were presented by the following: Dr. N. Cardoe (*London*), Dr. R. K. W. Kuipers (*The Hague, Holland*), Mr. J. Charnley, Prof. J. H. Kellgren (*Manchester*), Dr. J. J. de Blécourt (*Groningen, Holland*), Dr. N. Swanson (*Toronto*), Dr. W. R. C. Alexander and Dr. J. J. R. Duthie (*Edinburgh*), Dr. H. Duncan and Dr. A. St. J. Dixon (*Hammersmith*), and Dr. F. Françon (*Aix-les-Bains*).

The Heberden Round was conducted by Prof. E. G. L. Bywaters at the Postgraduate Medical School, Hammersmith, on October 2, 1959 (*Annals*, **18**, 330). Communications were received from Prof. E. G. L. Bywaters, Dr. B. W. D. Badley, Dr. B. M. Ansell, Dr. A. St. J. Dixon, Dr. J. T. Scott, and Dr. D. Rix (*Hammersmith*), followed by demonstrations by Prof. E. G. L. Bywaters, Dr. B. M. Ansell, Dr. J. T. Scott, and Dr. J. Griffin.

The Heberden Oration for 1959 was delivered on December 4, 1959, by Prof. A. Neuberger, F.R.S., of the Department of Chemical Pathology, St. Mary's Hospital, at the Wellcome Foundation, London, on "The Proteins of Connective Tissue and their Metabolism" (*Annals*, **19**, 1).

Professor Neuberger was presented with the Heberden Medal for 1959 by the President.

The Annual Dinner was held on December 4, by kind permission of the Master, at the Hall of the Worshipful Society of Apothecaries, London. Among the guests present were Sir Raymond and Lady Streat, Prof. and Mrs. W. Mansfield-Cooper, Sir Robert and Lady Platt, Dr. T. F. Fox, Dr. H. A. C. Clegg, and Prof. and Mrs. Neuberger.

The Annual General Meeting was held on December 4 and 5, at the Wellcome Foundation, London.

The clinical meeting which followed is reported below (p. 61).

Grant-in-Aid

The Society acknowledges with appreciation the renewal of a grant from the Empire Rheumatism Council.

Library

The Society is indebted to the Ciba Foundation for their kindness in housing the Library at 41 Portland Place, London, W.1.

The Honorary Librarian, Dr. W. S. C. Copeman, reports that the most important event of the year has been the re-cataloguing of the whole library under the expert supervision of Dr. F. N. L. Poynter, the librarian of the Wellcome Historical Medical Library. It is hoped that the new catalogue will go to the printers within the next few weeks. It will be circulated to all members of the Society as soon as it is complete. Since the first edition of the catalogue in 1954, 88 new works have been added to the library as well as an original letter of William Heberden. Amongst the important additions during the past year is the extremely rare little book of advice to the gouty entitled *Consilium Podagricum*, by Elias Anhart von Gratz, which was published at Ingollstadt in 1581.

The Wellcome Trustees have continued support financially both in the purchase of books and by arranging to have the books inspected, cleaned, and bound when necessary. We are enormously indebted both to the trustees and to Dr. Poynter and the staff of his library.

The Society has, in common with other societies possessing an historical interest, affiliated with the new

Faculty of the History of Medicine and Pharmacy which has been inaugurated by the Worshipful Society of Apothecaries of London. It is hoped that members of the Society who have any books or items of rheumatic interest prior to 1914 will present or loan them to the library.

OFFICERS FOR 1960

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Dr. F. Dudley Hart, F.R.C.P.,
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M. C. G. Andrews
(Tel. No.: COVent Garden 0871.)

PROGRAMME FOR 1960

Clinical Meeting at the West London Hospital on February 26.

Clinical Meeting at Manchester University on July 1 and 2.

Heberden Round at the London Hospital, conducted by Dr. W. S. Tegner, on September 23.

Heberden Oration, Annual General Meeting, and Dinner on December 2 and 3.

Titles and short programme notes of original communications which Members wish to make to the Society during 1960 should be sent to the Senior Hon. Secretary (Dr. Malcolm Thompson, M.R.C.P., Physical Medicine Department, Royal Victoria Infirmary, Newcastle-upon-Tyne) at least one month before the date of the meeting. Abstracts for publication in the *Annals of the Rheumatic Diseases* (approximately 300 words) should be sent in advance or handed to the secretary at the meeting. Additional meetings will be arranged if necessary.

Annual General Meeting.—The following communications were presented:

Erythrocyte Survival in Rheumatoid Arthritis. DR. S. M. LEWIS AND DR. I. PORTER (*Hammersmith*) (Introduced) (p. 54).

***Post mortem* Studies of Movement in the Cervical Spine.** DR. J. BALL AND DR. K. A. E. MEYERS (*Manchester*): The degree of angular movement of the cervical vertebrae (C.2-7) between the flexed and extended position of the spine was measured after applying loads of up to 4,000 g. to the atlas, the first dorsal vertebra being fixed.

In radiologically "normal" adult spines, movement at the first (C.2-3) and sixth (C.7/D.1) disks was less than at other levels; peak movement commonly occurred at the fourth (C.5/6) disk.

Removal of the "posterior segment" (laminae, spinous processes, and attached ligaments) and the interfacetal joints in radiologically normal spines resulted in progressive increase in angular mobility. These structures thus took some of the strain imposed in flexion-extension. The ligaments of the "posterior segment" and the capsules of the interfacetal joints in *mobile* spines in rheumatoid arthritis (2 cases), Reiter's disease (1 case), and ankylosing spondylitis (1 case) appeared to behave as in normal spines.

There was some evidence that reduced mobility in one part of the spine was associated with increased mobility elsewhere; this was observed in disk degeneration (reduced movement at lower disks) and in a case of Reiter's disease with reduced mobility at the upper disks. After removal of the "posterior segment" and the interfacetal joints, the "disk apparatus" in normal and degenerate spines was still often capable of withstanding flexion loads of 4,000 g. This was probably largely due to the posterior longitudinal ligament, since (*a*) in degenerate spines most of the disk fibres joining the vertebrae had been replaced by friable debris, and (*b*) after removal of the posterior longitudinal ligament, the normal disk often ruptured with relatively small flexion loads. Rupture induced in this way in a normal disk characteristically occurred at the junction of the disk and the upper vertebral plate and was unaccompanied by forward dislocation. If, however, the posterior longitudinal ligament and the posterior part of the disk were severed with the interfacetal joints intact, some forward subluxation tended to occur; even after complete severance of disk and longitudinal ligaments, the interfacetal joint capsules might prevent complete dislocation when a flexion load of 4,000 g. was used—the effect in this situation being a severe anterior subluxation. It would seem, therefore, that the posterior longitudinal ligament and the capsule of the interfacetal

joints protected, in some degree, the disk annulus against severe flexion-extension loads.

Preliminary experiments indicated that the interfacetal joint capsules protected the disk annulus against torsional loads. However, the longitudinal ligaments (anterior and posterior) appeared to offer no such protection for, in the absence of the interfacetal joints, it had been possible to induce rupture of the disk with torsional loads, in the presence of intact longitudinal ligaments; the possible importance of torsional loads as a cause of annulus tears appeared to require further study.

The interspinous ligaments and ligamentum flavum together exhibited rubber-like elasticity. But the elasticity of these ligaments was variable. From measurements in thirteen cervical spines, a positive correlation had been found between total flexion-extension mobility of the intact spine and the extensibility of these ligaments. This relationship had been observed in young and old adult subjects and in radiologically normal and diseased spines; it was thought to represent an adaptational change in the ligaments following alterations in mobility. Preliminary histological studies of the ligamentum flavum revealed no obvious explanation for the observed variations in extensibility.

Discussion.—PROF. E. G. L. BYWATERS (*London*) congratulated the authors on their detailed exposition of this subject, and asked whether they had reached any conclusions regarding the mode of origin of subluxations that occurred in the cervical spine in rheumatoid patients?

DR. BALL replied that the posterior longitudinal ligament must be involved, possibly by the neighbouring granulomatous process. Several more experiments were needed before they could be sure that they need not incriminate inter-facetal joint capsules. It seemed that these capsules had to be abnormal before a forward slipping of a bone like the atlas occurred. In the rheumatoid spine it was possible that anterior and posterior ligaments might both be involved, and in these circumstances a load on the atlas could produce a controlled subluxation, characteristic of the rheumatoid cervical spine.

DR. R. HARRIS (*Buxton*) remarked that these were small loads (4 kg.), equivalent to the weight of the head. He imagined that higher loads would be involved in traumatic subluxations, possibly with different results.

DR. BALL replied that the actual degrees of movements produced in these experiments were very close to what many would have observed in forced flexion and extension in man. From that point of view the sort of observations they had made would be relevant to those in man.

PROF. J. H. KELLGREN (*Manchester*) said that in the rheumatoid knee increased lateral and anterior-posterior mobility was often found without gross destruction of cartilage, which must be related in some way to the articular ligaments. This relaxation of ligaments was something not much was known about.

PROF. E. G. L. BYWATERS (*London*) asked whether the authors thought that with primary loss of disk space, due to whatever cause, the interfacetal joints acted as a pivot on the two vertebrae, so that one side of the interfacetal joint would not stretch, and might so cause changes in the tensile strength of the interfacetal ligaments. (No reply.)

Benign Polyarthritis. DR. J. S. LAWRENCE (*Manchester*) (p. 20).

Serum Cholesterol Levels in Generalized Osteo-Arthrosis. PROF. J. H. KELLGREN, MISS J. V. HEWITT, AND DR. J. S. LAWRENCE (*Manchester*): The relationship between serum cholesterol levels, radiological signs of osteo-arthrosis in the hands, and obesity, was studied in a random population sample of 1,200 people from the town of Leigh. The incidence of all three features rose with age in both sexes, but the serum cholesterol showed a tendency to fall in men over 60 years and in women over 70 years, and the prevalence of obesity was also reduced in old age. Osteo-arthrosis of the hands was more prevalent in the obese than in the non-obese in both sexes, and in subjects with above average levels of serum cholesterol. However, the relationship between osteo-arthrosis and serum cholesterol was less apparent in the small group with serum cholesterol levels over 360 mg. per cent. The associations between serum cholesterol and osteo-arthrosis, and between obesity and osteo-arthrosis, were greater than the rather slight association noted between obesity and serum cholesterol.

Discussion.—DR. A. G. S. HILL (*Stoke Mandeville*) asked whether there was any relationship between osteo-arthrosis and hypertension.

PROF. KELLGREN said that he could not answer until the data had been tabulated.

DR. LAWRENCE said that Dr. Lewis-Faning and Dr. Fletcher had investigated this aspect, and that the answer was No.

PROF. E. G. L. BYWATERS (*London*) asked whether it would not be more correct to say that "female men" were like mice. A marked sex difference had been shown.

PROF. KELLGREN replied that sex difference worked two ways. In women the cholesterol level appeared important, in men the obesity. The question of lipid metabolism could not be ignored in the study of osteo-arthroses.

DR. R. HARRIS (*Buxton*) asked if there would be any advantage in taking fat-fold thickness measurements?

PROF. KELLGREN said that they had considered it but that it was not convenient to do on a survey as measurements would have to be done on various parts of the body and the patients did not like them.

DR. W. A. BOURNE (*Hove*) asked whether there was any relation to vascular disease.

PROF. KELLGREN replied that to compare their findings with coronary disease would imply a different survey altogether.

Latex Slide Test in Rheumatoid Arthritis and Allied Conditions. DR. J. V. WILSON, DR. R. A. H. MORRISON, AND DR. C. N. WATSON (*Harrogate*): A comparison was made of the results obtained in a series of over 500 consecutive patients in whom both Rose-Waaler (differential agglutination test) and latex slide tests for the rheumatoid factor had been performed. The latex slide test, which

could be done as a simple side-room test, was considered to be fully reliable and useful as a routine screening test in patients suspected to be suffering from rheumatoid arthritis. (No discussion.)

***Haemophilia and Haemophilic Arthropathy, Historical Aspects and a Review of 42 Cases of Haemophilia with Particular Reference to Haemophilic Arthropathy.** DR. J. WEBB AND DR. A. ST. J. DIXON (*London*).

***Arthritic Manifestations of Erythema Nodosum.** DR. L. H. TRUELOVE (*Edinburgh*) (Introduced).

Antibodies against Nuclear and Cytoplasmic Cell Constituents in Systemic Lupus Erythematosus and Other Diseases. DR. G. ASHERSON (*Taplow*): Observations were made on the complement-fixing antibodies against human and animal tissues found in the serum of patients with systemic lupus erythematosus, lupoid hepatitis, and primary biliary cirrhosis. Serum complement levels were also estimated in twelve patients with systemic lupus erythematosus.

Of 25 patients with systemic lupus erythematosus, four had complement fixing antibodies against rat liver nuclei, rat liver cytoplasm and calf thymus desoxyribose nucleic acid, five had antibodies against mitochondria and soluble cellular protein, and six against mitochondria alone. Ten of the sera failed to react with any of the antigens.

The occurrence of low serum complement levels in eight out of twelve patients suffering from systemic lupus erythematosus provided evidence that the complement fixing antibodies could combine with their corresponding antigens *in vivo*. The findings supported the view that systemic lupus erythematosus was a disease characterized by multiple anomalous auto-antibody formation.

Discussion.—DR. W. R. M. ALEXANDER (*Edinburgh*) said that he did not wish to appear "anti-complimentary", but he thought that Dr. Asherson was rather rash in suggesting that the finding of a low serum complement in systemic lupus implied fixation in tissues. He agreed that the serum in systemic lupus contained factors—such as anti-nuclear factor—which might be termed auto-antibodies in that they combined specifically with cell components. This had not, however, been shown to occur *in vivo*. Also, in a survey of about 700 sera, he had shown anti-nuclear factor to be present in many human sera, including 60% of cases of rheumatoid arthritis. It had also been demonstrated in four or six healthy dogs. Dr. Alexander suggested that this factor might be a normal component of serum which was increased in certain diseases. If so, it seemed unlikely to be causally related to the lesions in lupus erythematosus.

PROF. E. G. L. BYWATERS (*London*) said that most people who had investigated complement in disease had been cautious in attributing particular levels to particular processes. It was really only possible to be certain of that after experimental studies of actual complement levels had been done in different patients.

DR. J. J. R. DUTHIE (*Edinburgh*) said that even if they accepted that antibodies appeared *in vivo*, they might still be the product of some damaging process which altered these tissues, making them antigenic, and might have no connexion with the pathogenesis of the disease.

DR. J. BALL (*Manchester*) asked whether using the analogous situation in syphilis, Dr. Asherson believed in an auto-immune basis for chronic syphilis.

DR. ASHERSON replied that it had not been excluded that the formation of these antibodies was secondary to tissue damage but he favoured the view that they were a manifestation of the immunological abnormalities underlying the disease. Indeed one of the striking features of systemic lupus erythematosus was the finding of multiple antibodies and it was reasonable to suggest a primary abnormality of the antibody-producing mechanism. It might be true that the Wassermann antibody was responsible for tissue damage in syphilis but he did not hold that view. He agreed that it would be desirable to measure the rate of formation and destruction of the serum complement components. Other workers had correlated low serum complement with disease activity in systemic lupus erythematosus.

***Nail Growth Studies in Rheumatoid Arthritis and Still's Disease and Response to Treatment.** DR. E. B. D. HAMILTON (*Taplow*) (Introduced).

Vascular Channels from Bone Marrow to Periosteum. PROF. R. G. HARRISON (*Liverpool*), DR. C. B. HEALD, AND DR. A. C. ELKIN (*London*): The fate of solutions or suspensions injected into periosteum or the superficial aspect of bone clearly depended on several factors, not the least important of which was the direction of blood flow between periosteum, underlying bone, and any attached muscles. Until recently it was taught that bone vascularization was aided by a centripetal flow of arterial blood from periosteum to subjacent bone. On this theory any fluid introduced into periosteum, or the bone immediately subjacent to it, would be expected to pass into bone at the site of injection. Earlier experiments had demonstrated that radiopaque solutions and suspensions introduced by a needle perforating the compactum and well imbedded in the underlying cancellous bone in the cadaver were rapidly removed directly outwards, through the bone. Clinical investigations had also demonstrated that fluids introduced into the periosteum, or cancellous bone immediately below the compactum, passed out from the bone surface into attached muscles, so producing a "spray effect" radiographically. This had been confirmed, following the injection of Hypaque and indian ink, by radiographic and histological examination of the acromion process and lateral epicondyle of the cadaver of a man aged 67 who died from carcinoma of the oesophagus. Histologically, the indian ink flowed out from the site of injection into the interfascicular spaces of the muscles taking origin from these sites. The direction of flow of injected fluid outwards from the surface of bone was understandable on the basis of recent researches which had demonstrated that vascular channels connecting the periosteum with the subjacent cortex of *normal* bone were venous in nature, and con-

* To appear in the June, 1960, issue of the *Annals*.

ducted blood centrifugally into the overlying periosteal capillary bed.

Discussion.—DR. J. J. R. DUTHIE (*Edinburgh*) suggested a point of clarification. The sections seemed to show material lying outside the blood vessels after injection into the periosteum, but the bone perfusion studies showed the material in capillaries in the muscles.

PROF. HARRISON said that substances injected through the periosteum could get out of the bone and then pass into the interfascicular space. The reason was that the venous pressure was higher on the inside of the bone than on the outside, so that it must come out. Once it came into the muscle the majority lay in the interfascicular space.

PROF. E. G. L. BYWATERS (*London*) said that, regarding the very interesting pictures showing direct intramuscular injection and the spray effect, it was difficult to believe that this was entirely in the extravascular space and none in the lymph channels or blood vessels. He remembered some years ago that Edholm measured bone blood flow with particular reference to Paget's disease where there was a large blood flow, and also in some normal subjects, and he did not know whether this technique had been used since. He wondered whether Prof. Harrison had any information about relative amounts of venous flow from the surface of a long bone, like the tibia, *via* the periosteum and epiphyseal vessels.

PROF. HARRISON replied that the difference in radiological appearance between material injected directly into muscle and that after injection into bone, probably resulted from the fact that after an injection into muscle, the injection material presumably remained localized, whereas after an injection into periosteum it was possible for the substance to percolate out and give a spray effect. Measurements of blood flow had been made by da Costa, who gave figures for venous drainage from bone which were greater than from skin. He himself had not made direct measurements of venous blood flow.

2-4-6 Trihydroxybenzoic Acid in the Treatment of Rheumatic Fever. DR. E. B. D. HAMILTON AND PROF. E. G. L. BYWATERS (*Taplow*) (p. 52).

NEW ZEALAND RHEUMATISM ASSOCIATION

ANNUAL REPORT, 1959

The 12th Annual General Meeting of the New Zealand Rheumatism Association was held at Queen Elizabeth Hospital, Rotorua, on October 29, 1959. The Chairman, Dr. Rowatt Brown, and 22 members were present.

Appreciation was expressed at the generosity of the Empire Rheumatism Council in making two Travelling Fellowships available to Australasia on alternate years.

Ways and means of furthering the establishment of a New Zealand Branch of the Empire Rheumatism Council as a combined lay and professional body were discussed.

An Advisory Committee to consult with Sir Horace Smirk on medical research at the Otago Medical School was appointed.

The following Clinical Papers were given:

SIR CHARLES BURNS: **Personal Experiences in Collagen Disorders.**—Attention was drawn to clinical and laboratory findings such as are within the reach of every practitioner making a day-to-day examination which should lead to a diagnosis of collagen disorder. A Pel–Ebstein like temperature chart and high erythrocyte sedimentation rate were mentioned. In none of the cases presented had the L.E. phenomenon been observed. Improvement on steroids had been noted and relapse when the steroids were withdrawn. Long remissions occurred in some cases. Psychotic states and the collapse of a vertebra had been noted when on steroid therapy.

DR. J. VALENTINE: **Diagnostic Difficulties in Arthritis with Consequent Difficulties in Management.**—An analysis of 166 consecutive patients admitted to Queen Elizabeth Hospital showed that 150 suffered from arthritis and sixteen from allied disorders. Of the 150 cases of arthritis, the final diagnosis was rheumatoid arthritis in 68·7 per cent.; of the remainder 14 per cent. were diagnosed as osteo-arthritis probably combined with rheumatoid arthritis. These cases were discussed and it was considered that either many cases are of mixed origin or the criteria of the American Rheumatism Association are not sufficiently discriminatory.

Because of the mixed nature of many cases, treatment should be so ordered that it will benefit every aspect of the disease. The active approach by physiotherapy and occupational therapy is advocated, drugs being used only for pain relief. Intra-articular hydrocortisone should be used freely to enable more active joint movement with less pain.

DR. B. S. ROSE and DR. I. C. ISDALE: **Gout among the Maoris.***

MR. R. NICHOLSON: **Suppurative Arthritis as a Complication of Systemic Steroid Therapy.**—Three cases of septic arthritis occurring as a complication of oral steroid therapy for dermatological conditions were presented.

In all cases there was little sign of systemic infection and the temperature was only slightly elevated but the

* To appear in the June, 1960, issue of the *Annals*.

erythrocyte sedimentation rate was raised in each case. The organism in two cases was identified as staph. aureus. The cases emphasized the difficulty in diagnosis and the advisability of joint aspiration or biopsy to confirm the diagnosis.

DR. T. HIGHTON: **On the Shrinkage Temperature of Collagen in Rheumatoid Arthritis, Scleroderma, and Other Conditions.**—An apparatus for determining the shrinkage temperature of collagen on a biopsy specimen was described. Normal values for the shrinkage temperature of human collagen from different sites and at different ages was given. Variations from the normal, *e.g.* in rheumatoid arthritis, were described. A biological pattern in the shrinkage temperature of collagen from other species was demonstrated. The possible implications of these findings were discussed.

DR. C. GRESSON: **Angiomatous Rheumatism.**—A case of angiokeratoma corporis diffusam (Falry) occurring in a 37-year-old male was described, with a detailed account of the rheumatic disability. Renal biopsy findings were illustrated. The relationship of the inborn error of metabolism to the angiomas and to the rheumatic pains was discussed.

DR. C. ALEXANDER: **Some Points in the Radiology of the Rheumatic Disorders.**—This paper stressed the degree to which technical aspects affect the usefulness of radiology and the need of technique to the clinical picture. The need for a control film of the normal side in suspect rheumatoid arthritis and tuberculosis, the value of *x*-raying both hands and feet in any doubtful arthritis, the value of a weight-bearing lateral film of the feet and of tomography of the spine were discussed and illustrated.

The radiological findings in collagen and rheumatic diseases, shoulder degeneration and Caisson disease were discussed. The concept of osteo-arthritis as impairment of cartilage elasticity due to stress (Hersche, 1954) and the demonstration of cartilage changes after denervation (Acheson, 1958) were described and related to the radiological findings.

The conditions simulating ankylosing spondylitis were discussed and the suggestion was made that ankylosing spondylitis and Reiter's syndrome were in fact opposite poles of the same disease.

A clinical demonstration of cases was arranged by the staff of the Queen Elizabeth Hospital, and the following papers were also presented:

DR. K. IBBERTSON: **Disorders of Calcium Metabolism in Bone and Their Treatment.**

DR. B. ROSE and DR. I. C. ISDALE: **Agglutination Tests for Rheumatoid Arthritis.**

BRAZIL

To celebrate the 10th anniversary of the rheumatism department of the General Hospital in Rio de Janeiro, presided over by Professor Pedro Nava, the Journal *Brasil-Médico* has issued a special number. This contains full reports of the ten symposia held in his honour, each presided over by a physician distinguished in the field of rheumatology.

The subjects are: The Field of Rheumatology (Dr. Jacques Houli); Rheumatoid Arthritis (Dr. Waldemar Bianchi); Infective and Allergic Arthritis and the Para-Rheumatic Inflammatory Disorders (Dr. Pedro Nava); Osteo-arthritis (Dr. Da Silva); Gout and Metabolic Arthropathy (Dr. I. Bonomo); Non-Articular Rheumatism (Dr. H. Seda); Vertebral Arthrosis (Dr. C. V. Nunes); Ankylosing Spondylitis (Dr. N. Senise); and Rheumatic Disease as a Social Problem (Dr. D. Olinto). W.S.C.C.

VI INTERNATIONAL CONGRESS OF INTERNAL MEDICINE

Basel, 1960

The VI International Congress organized by the International Society of Internal Medicine (President: Sir Russell Brain) will be held on August 24-27, 1960, at Basel, Switzerland, under the presidency of Prof. A. Gigon.

The principal subjects will be: Pathogenesis and Treatment of Oedema and Clinical Enzyme Tests.

Panel discussions will be held on: Interstitial Nephritis, Nephrosis, Diuretics, Enzymology, Serology of Rheumatic Disease, Instruction in Internal Medicine.

The official languages are German, French, and English. Programmes and registration forms (to be completed by April 30) may be obtained from the Congress Secretary:

Prof. Dr. H. Ludwig,
Steinentorstrasse 13,
Basel 10, Switzerland.

Ann. rheum. Dis. (1960), **19**, 66.

ABSTRACTS

This section of the ANNALS *is published in collaboration with the two abstracting Journals,* ABSTRACTS OF WORLD MEDICINE, *and* OPHTHALMIC LITERATURE, *published by the British Medical Association.*

The abstracts selected for this Journal are divided into the following sections: Acute Rheumatism; Chronic Articular Rheumatism (Rheumatoid Arthritis, Osteo-Arthritis, Spondylitis, Miscellaneous); Disk Syndrome; Gout; Pararheumatic (Collagen) Diseases; Non-Articular Rheumatism; General Pathology; ACTH, Cortisone, and other Steroids; Other General Subjects. At the end of each section is a list of titles of articles noted but not abstracted. Not all sections may be represented in any one issue.

The section "ACTH, Cortisone, and other Steroids" includes abstracts and titles of articles dealing with research into the scope and modus operandi *of steroid therapy.*

Acute Rheumatism

Controlled Study of Three Methods of Prophylaxis against Streptococcal Infection in a Population of Rheumatic Children. II. Results of the First Three Years of the Study, including Methods for Evaluating the Maintenance of Oral Prophylaxis. FEINSTEIN, A. R., WOOD, H. F., EPSTEIN, J. A., TARANTA, A., SIMPSON, R., and TURKEY, E. (1959). *New Engl. J. Med.*, **260**, 697. 9 refs.

From New York University College of Medicine comes this further report of the results in 391 children and adolescents who had had unequivocal attacks of rheumatic fever and who have been followed up in a special prophylaxis clinic, the aim being to compare the effectiveness of three prophylactic regimes. An earlier report presenting the results of the first 2 years of this study appeared in 1957 (Wood and others, *New Engl. J. Med.*, **257**, 394; *Abstr. Wld Med.*, 1958, **23**, 200). It is recalled that the three regimens were as follows:

(1) 1 g. sulphadiazine daily by mouth in a single dose;
(2) 200,000 units buffered potassium benzylpenicillin daily by mouth in a single dose half an hour before breakfast;
(3) 1,200,000 units benzathine benzylpenicillin given by intramuscular injection every 4 weeks.

In the first 2 years of the study the attack rates for streptococcal infections per patient-year in the three groups were 24, 20, and 7 per cent. respectively, while the rates for recurrence of the rheumatic fever were 2·7 per cent., 4·8 per cent., and *nil* respectively.

In the present study, therefore, an attempt was made to ascertain whether the superiority of parenteral penicillin might have been due in part to the oral prophylaxis not having been faithfully carried out. Two procedures were adopted:

(1) A special interview with each patient, on the basis of which prophylaxis was considered "good" if fewer than five non-consecutive daily doses had been missed during a month;
(2) The patient was supplied each month with a bottle containing a known number of the pills or tablets, prophylaxis being considered "good" if the number of unused pills or tablets returned differed from the expected number by −3 to +4 for penicillin tablets, or by −3 to +9 for sulphadiazine tablets.

From the results of the interview good prophylaxis was apparently achieved by 75 per cent. of patients taking oral penicillin and by 67 per cent. of those taking sulphadiazine; by the pill count technique prophylaxis was assessed as good in 55 per cent. of patients taking penicillin and in only 44 per cent. of those given sulphadiazine. The accumulative findings for the first 3 years of this study showed that the incidence of streptococcal infections per patient-year was now 21, 20·7, and 7·3 per cent. respectively, while the recurrence rate of rheumatic fever per patient-year was 1·9, 5, and 0·3 per cent. respectively.

The authors' main conclusions are as follows:

(1) That 1,200,000 units benzathine benzylpenicillin given intramuscularly every 4 weeks is more effective in preventing both streptococcal infection and recurrence of rheumatic fever than either of the two methods of oral prophylaxis.
(2) The results in the three groups showed little variation even when the oral prophylactic regimen had been faithfully followed.
(3) Oral sulphadiazine is approximately equal in effect to oral penicillin in the prevention of streptococcal infections, but is superior to oral penicillin for the prevention of rheumatic fever in patients maintaining good prophylaxis.

Kenneth Stone.

Prognostic Significance of Valvular Involvement in Acute Rheumatic Fever. FEINSTEIN, A. R., and DI MASSA, R. (1959). *New Engl. J. Med.*, **260**, 1001. 25 refs.

At the Irvington House Prophylaxis Clinic, New York University College of Medicine, 359 patients were observed in their first attack of rheumatic fever and were then followed up for 2 to 9 years (average 4·7 years).

They have been examined at monthly intervals and have received continuous antimicrobial prophylaxis.

It was found that definite evidence of cardiac enlargement, congestive heart failure, and pericardial friction rubs occurred almost exclusively in patients who had valvular involvement [this term is fully defined in the paper]. Prolongation of the P-R interval occurred with almost equal frequency in these groups—that is, those with "valvulitis", "probable valvulitis", and "no valvulitis"—but showed no correlation with the subsequent cardiac status. Thus, of those who in the acute stage had valvulitis 67 per cent. (86 of 123) ended up with permanent heart disease, as compared with only 25 per cent. (13 of 52) of those with probable valvulitis and none out of the 178 who had no valvulitis. It is concluded that the auscultatory findings present during the acute attack of rheumatic fever are of primary importance in predicting the cardiac prognosis.

[The abstracter agrees with these findings and conclusion, subject to limitations of the medium-term follow-up. Later the situation may not necessarily remain the same.] *John Lorber.*

Studies of Acute Rheumatic Fever in the Adult. I. Clinical and Laboratory Manifestations in Thirty Patients. PADER, E., and ELSTER, S. K. (1959). *Amer. J. Med.*, **26**, 424. 11 figs, 25 refs.

The manifestations of acute rheumatic fever in the adult are described with reference to the findings in 30 patients (12 male and 18 female) aged 21 to 59 seen at Mount Sinai Hospital, New York, between 1952 and 1957. Symptoms in 28 of the thirty cases fulfilled the criteria laid down by Duckett-Jones for the diagnosis of rheumatic fever; in the remaining two cases the condition was diagnosed post mortem. Of the thirty patients, seventeen of whom were Puerto Ricans, fourteen were seen in what was thought to be the first attack, while another fourteen were known to have had rheumatic heart disease preceding the acute episode. In eighteen there was a history of an upper-respiratory infection preceding the onset of rheumatic fever, but none of these had had adequate antistreptococcal treatment. Joint involvement was the most frequent manifestation and was usually a classic migratory polyarthritis. In a series of tables the authors analyse the nature and distribution of the joint involvement and the incidence and various manifestations of carditis, the laboratory findings, and the response to treatment. Details are given of five illustrative cases. In strong contrast to the findings in juveniles, none of the adults in this series had erythema marginatum, subcutaneous nodules, or chorea. Rheumatic fever in these adults also differed from that in children in showing a higher incidence of arthritis than of carditis. *E. G. L. Bywaters.*

II. The Rebound Phenomenon. ELSTER, S. K., and PADER, E. (1959). *Ann. intern. Med.*, **51**, 339. 3 figs, 33 refs.

This study of 43 patients with rheumatic fever, seen at Mount Sinai Hospital, New York City, between 1952 and 1957, was undertaken to determine the incidence, character, causation, and management of the "rebound" phenomenon, that is, the reappearance of clinical or laboratory signs of the disease after the termination of apparently successfully suppressive treatment. All 43 patients, most of whom were over 20 years of age, fulfilled the Duckett-Jones diagnostic criteria. Rebound was defined as the appearance of fever, an increased erythrocyte sedimentation rate (E.S.R.), reappearance of C-reactive protein, arthralgia, arthritis, chest pain, pericarditis, electrocardiographic abnormalities, or cardiac failure.

Of the 43 patients, 22 (51 per cent.) showed the rebound phenomenon, eight developing two "rebounds" and one four. These were most commonly manifested by fever (81 per cent.) and tachycardia (69 per cent.), and less frequently by arthralgia (56 per cent.) or arthritis (25 per cent.), while two patients developed pericarditis and five electrocardiographic abnormalities. The E.S.R. became abnormal in 97 per cent. and C-reactive protein reappeared in the serum in 92 per cent. In only two cases did the evidence of rebound depend on laboratory findings alone. In relation to drug treatment it was noted that rebound occurred in nine out of 22 patients treated only with salicylates, in seven out of twelve treated with steroids alone, and in six of nine treated by both methods. Rebound was also most frequent in those patients treated with steroids in high dosage. It did not seem to be related to duration of treatment, but only three of the patients were treated for more than 8 weeks. Abrupt or gradual cessation of therapy made little difference to the incidence, although this seemed to be lower following abrupt withdrawal of salicylates than of steroids. The rebound usually appeared on the first day after withdrawal, but in some cases was delayed until the 7th day, and lasted (in the absence of re-treatment) for periods varying between one and 29 days, the fever being short lived and abnormal laboratory findings being longer lasting. Second rebounds occurred more frequently in the steroid-treated group. The case history is presented of one patient with prolonged rheumatic fever and many rebounds who was finally discharged home taking aspirin, with a high E.S.R. and C-reactive protein in the serum after a period of 30 weeks in hospital.

The authors thus do not differentiate between relapse and rebound, believing them to be the same; nor do they consider that the phenomenon represents relative adrenocortical insufficiency (since it is seen with salicylates) nor part of a polycyclic attack. Dismissing also the theory of inadequately prolonged treatment, they incline to the view that the drugs alter the host's response to the basic pathogenic factor and conclude that the rebound phenomenon is an indication of persistent rheumatic activity necessitating re-treatment.

E. G. L. Bywaters.

Studies on the Occurrence of Bacteremia in Rheumatic Fever. MARIENFELD, C. J., SCHEFF, G., HACKETT, E., and JONES, D. (1959). *J. chron. Dis.*, **9**, 334. 2 figs, bibliography.

In this joint study carried out at Cook County Hospital, Chicago, by members of the medical schools of

Illinois and Chicago, 385 cultures were prepared from the blood of 185 children (aged 5 to 15) suffering from treated and untreated rheumatic fever in various stages and 124 cultures from that of one hundred untreated non-rheumatic patients of similar age who served as controls.

An unusual number of positive blood cultures were found in those suffering from rheumatic fever, the organisms being short-chained, Gram-positive streptococci, often diplococcal in form; this diplococcus was found in 66 per cent. of cases which had received no treatment in the acute stage, in 22 per cent. of those in the convalescent stage, and in 10 per cent. of those in the inactive stage. It was not isolated from any of the controls, among whom the percentage of positive blood cultures (including staphylococcal contaminants) was much lower. The cultures did not show any growth of diplococcus before at least 30 days of incubation. Few of the organisms produced haemolysis in the tube test, but several showed slight β-haemolytic activity on horse-blood-agar plates; the majority of positive cultures came from cases in which less than 30 days had elapsed since the onset of rheumatic fever. It is suggested that once rheumatic fever has been initiated by β-haemolytic streptococci the disease may be continued by this additional organism described, this suggestion being based on the clinical observation that a small number of patients with chronic relapsing rheumatic fever did not show an obvious response to large intravenous doses of penicillin; there is no evidence that the streptococcus becomes resistant to the antibiotic. The literature is extensively reviewed.

[The original paper should be consulted for details of the techniques employed.] *D. Preiskel.*

Clinical Observations on the Importance of Tonsillectomy in Rheumatic Fever. (Rilievi clinici sulla importanza della tonsillectomia nella malattia reumatica.) CASOLO, G., ORLANDI, G., PONZONI, C., and CINQUINI, U. (1959). *Reumatismo*, **11**, 196. 4 figs, 44 refs.

At the Ospedale Maggiore, Milan, the authors have studied the clinical course and changes in various laboratory findings in two groups of patients suffering from rheumatic fever, one of which had and the other had not undergone tonsillectomy previously. They arrive at the following conclusions:

(1) The macroscopic appearance of rheumatic tonsillitis, though not characteristic, is sufficiently constant in its morphological features to be recognizable.
(2) The morbid histology of the tonsils as a whole indicates the existence of a hyperergic inflammatory process such as may reasonably permit the suspicion of its rheumatic nature.
(3) Relapses of rheumatic fever are less frequent in patients who have undergone tonsillectomy.
(4) In such patients rheumatic relapses respond more promptly to cortisone therapy and the immunological responses return more rapidly to normal.
(5) In the authors' opinion tonsillectomy should be advised not only in the case of a first episode of rheumatic fever, but also in the case of relapses preceded or accompanied by tonsillitis.—[*From the authors' summary.*]

Prophylaxis of Recurrent Rheumatic Fever. (Prophylaxie des rechutes du rhumatisme articulaire aigu.) GIRAUD, P., BERNARD, R., HEURTEMATTE, A., SANSOT, M., LATIL, P., MAESTRAGGI, P., and MOINE, C. (1959). *Pédiatrie*, **14**, 337. 1 fig., 1 ref.

This paper records the results of penicillin prophylaxis in a group of children recovered from an attack of acute rheumatism in comparison with a similar group of children receiving no prophylaxis. The children were aged 3 to 16 years and the observations were continued for periods which varied from less than a year to 5 years. Among the treated children (210 in all), who received 600,000 units of benzathine penicillin intramuscularly every 10 to 15 days for a total period of 5,120 patient-months, there were three cases of relapse of acute rheumatism—a rate of 0·06 per 100 patient-months. Among the 190 children who received no prophylactic treatment after the initial attack and were followed up for a total of 8,282 patient-months there were thirty relapses—a rate of four per 100 patient-months. A smaller group of fifty children who received no specific prophylaxis, but were given "non-specific" prophylaxis in the shape of ultraviolet light, cod-liver oil, sea baths, or dietary supplements, was studied for 1,764 patient-months, 43 relapses being observed—a rate of 2·5 per 100 patient-months. The efficiency of penicillin prophylaxis is thus clear, but the general measures were also of some value.

The length of time for which prophylaxis with penicillin should be maintained is discussed and it is shown that the majority of relapses occur within 4 years of the last attack. It is therefore suggested that prophylaxis should be maintained for a minimum of 4 years. It is further suggested that after regular prophylaxis has ceased "prophylaxis on demand" should be arranged by ensuring that when any rheumatic child develops a febrile illness a dose of penicillin adequate to eliminate haemolytic streptococci from the throat should be given without waiting to determine whether or not such organisms are present. A mixture of 600,000 units of benzathine penicillin, 300,000 units of procaine penicillin, and 300,000 of benzylpenicillin is recommended.

C. Bruce Perry.

Effect of Large Doses of Prednisone on Acute Rheumatic Fever. FERENCZ, C., MARKOWITZ, M., and BUNIM, J. J. (1959). *A.M.A. J. Dis. Child.*, **97**, 561. 4 figs, 5 refs.

In order to evaluate the effect of prednisone in the treatment of rheumatic fever, seventeen children with clinical evidence of active rheumatic carditis of less than one month's duration were treated at various hospitals in Baltimore with large doses of the drug. [There was no control group treated concurrently by other methods.] A prolonged course of treatment—a duration of at least 14 weeks was chosen arbitrarily—was used in the hope

that the recurrence of symptoms on withdrawal would thereby be diminished. To ascertain whether prednisone could be given without causing serious electrolyte imbalance the diet was not restricted and no extra potassium was given. The daily dose of prednisone was maintained at 50 to 75 mg. for 9 weeks and was then gradually tapered off.

The initial response to treatment was as good as might have been expected with cortisone, but the carditis progressed in one case—that of a a 9-year-old girl who was treated for 28 weeks, during which mitral and aortic diastolic murmurs appeared which persisted for at least 2 years. At the end of 2 years four patients had definite and two doubtful evidence of cardiac sequelae; these included three with aortic incompetence. All patients developed toxic signs during treatment, moon face, abdominal fullness, striae, and hirsutism being almost invariably present and excessive gain of weight universal. In no case was there gross electrolyte imbalance, though the carbon dioxide combining power and the sodium content of the serum tended to be high and the potassium level to fall during treatment. Three children developed a considerable degree of hypertension, one of them, with a blood pressure of 158/118 mm. Hg, developed convulsions on the 27th day. (Another patient, not included in this series, developed gross hypertension which persisted for several weeks after stopping treatment despite the use of ganglion-blocking drugs.) After stopping treatment fifteen of the seventeen children had a recurrence of rheumatic activity which was often prolonged and severe, including the return of abnormal cardiac findings in nine cases. None of these children was given a second course of treatment. In one case latent tuberculosis was activated, requiring chemotherapy.

It is concluded that prednisone used in this energetic way will not prevent the cardiac sequelae of acute rheumatism in all cases, nor will it usually prevent relapse.

[This method of treatment is in sharp contrast with that used by Wilson and Lim (*New Engl. J. Med.*, 1959, **260**, 802; *Abstr. Wld Med.*, 1959, **26**, 305), who gave very brief courses of steroids and obtained much better results and fewer relapses. It is possible that the use of prednisone in high dosage for a very long period predisposes to relapses rather than prevents them.]

John Lorber.

Changes in the Fundus Oculi in Acute Rheumatism. (In Russian.) KUŠKIJ, R. O., MINIOVIČ, M. M., and MAKAROVA, A. A. (1959). *Klin. Med.* (*Mosk.*), **37**, 38.

On examination of the fundus oculi in a number of cases of rheumatic fever with carditis in which visual disorders occurred the authors observed certain changes affecting the retinal blood vessels and, to a lesser degree, the optic disks. In their opinion such changes represent a local manifestation of the general effect of the rheumatic process on connective tissue and, although not specific for rheumatic fever, they can nevertheless be used in assessing the activity of the disease.

In the acute stage of a primary or recurrent attack disturbances of blood flow in the retinal arteries were noted, associated with transitory changes in the vessels such as irregularity of outline and thickening of the walls. In some cases patches of white exudate occurred which were ill defined, soft, and fluffy, and situated around the optic disk. The disk itself was sometimes congested and sometimes had the appearance characteristic of optic neuritis. In patients observed after the acute attack had subsided the blood vessels showed an early sclerosis and the areas of exudate had become smaller and better defined. The congestion and inflammatory changes affecting the optic nerve sometimes developed into atrophy of the optic disk which gave rise to serious impairment of vision. Three illustrative cases are described in detail.

F. S. Freisinger.

Rheumatic Fever and the Thyroid Gland. [In Russian.] JASINOVSKU, M. A., and PEČENAJA, R. B. (1959). *Probl. Ėndokr. Gormonoter.*, **5**, 57. 2 figs, bibl.

In this report attention is drawn to the close relationship between acute rheumatism and thyroid dysfunction, which has been commented on by many observers, from Parry in 1872 to the present day. The results of observations on 1,600 patients have convinced the present authors that a distinct connexion exists between these two disorders. It has often been noted that rheumatism is frequently a precursor of Graves's disease, that acute thyroiditis often occurs in patients with acute rheumatism, and that during the course of Graves's disease in rheumatic subjects the onset of an acute attack of rheumatism may give rise to severe exacerbation of the thyroid symptoms. Vincent, who claimed to have found enlargement of the thyroid gland in some 67 per cent. of adult rheumatic subjects, stated as long ago as 1907 that absence of thyroid reaction in rheumatism indicated a poor prognosis. Other authors have described hypothyroidism or in some cases myxoedema as supervening on acute rheumatism.

Among the 1,600 cases of rheumatism seen by the authors at the Therapeutic Clinic, Odessa, between 1935 and 1955, symptoms of thyrotoxicosis were observed in about 10 per cent. of cases, this proportion rising in the post-war years to 16 or 17 per cent. Furthermore, of 74 patients with Graves's disease treated at this Clinic, nine gave a history of previous rheumatic polyarthritis and five had mitral valvular disease, while four more had mitral valvular disease without a history of acute polyarthritis. Increased absorption of radioactive iodine was observed in twelve out of 33 cases of rheumatism so tested; while of twenty cases of acute rheumatism in which the basal metabolic rate was determined it was raised in all, though clinical symptoms of thyrotoxicosis were found in only five. A further significant point was that in many of these cases antirheumatic treatment alone (aspirin or salicylates) banished or greatly relieved the thyrotoxic symptoms.

The incidence of myxoedema following rheumatism was much lower in this series than that of thyrotoxicosis. Two such cases are reported; in one of these patients, who had two attacks of acute rheumatic polyarthritis,

myxoedema developed during pregnancy 4 years after the second attack, while the second patient developed myxoedema 1½ years after the first attack and 2 years before the second; both of these patients had also mitral involvement. While vigorous treatment of the rheumatic condition usually sufficed to allay the symptoms of thyrotoxicosis, repeated relapses of rheumatism in some cases led to the establishment of a stable toxic goitre, necessitating partial or subtotal thyroidectomy. The two patients with myxoedema required prolonged thyroid medication—in one case for 10 years. Among the hazards of uncontrolled rheumatism, therefore, must be included thyroid dysfunction, with the possibility of permanent structural and functional change in the gland, this being usually hypertrophic but occasionally atrophic in type.

L. Firman-Edwards.

Relation of Isolated Recurrences of Sydenham's Chorea to Preceding Streptococcal Infections. TARANTA, A. (1959). *New Engl. J. Med.*, **260**, 1204. 4 figs, 19 refs.

From New York University College of Medicine the author reports a study of sixty children with a history of chorea who were followed up by monthly examinations for 2 to 67 months (mean 40·7 months) at the Irvington House Rheumatic Fever Prophylaxis Clinic, Irvington-on-Hudson, with the aim of elucidating the relation between streptococcal infection, rheumatic fever, and chorea. At some time during the preceding 28 months all but two of the patients had had rheumatic fever (as defined by modified Duckett-Jones criteria), and two exceptions having had only chorea. Each was given continuous prophylactic antistreptococcal treatment and at each visit a throat swab was taken, while the antistreptolysin-O and antihyaluronidase titres were determined at least every 2 months.

Of the sixty children, 41 developed no streptococcal infection during the follow-up period and there was no recurrence of chorea in these patients. The remaining nineteen patients, however, developed such infection despite the prophylactic regimen, and in three of these the chorea recurred, in one case twice. It is of interest to note that these four recurrences took place at intervals after the development of streptococcal infection (as judged by the rise in antibody titre) of approximately 5, 70, 90, and 180 days respectively, with a mean of about 87 days. These periods are contrasted with the mean interval of 10 days between the rise in antibody titre and the onset of polyarthritis or carditis in the 29 children who, despite prophylaxis, suffered a recurrence of rheumatic fever. Detailed case reports are given of the three children, in whom, it was observed, the recurrence of chorea was not preceded or accompanied by clinical evidence of rheumatic fever. Only one of the four recurrences was associated with a high erythrocyte sedimentation rate and a positive result in the test for C-reactive protein in the absence of clinical signs. These findings thus provide the first reported evidence that Sydenham's chorea can follow Group-A streptococcal infection at longer intervals than, and in the absence of, polyarthritis and carditis, and indeed in the absence of any sign of "rheumatic activity".

E. G. L. Bywaters.

Effect of Prednisone and Dexamethasone on Capillary Permeability in Rheumatic Fever. (Effetto del prednisone e del desametasone sulla permeabilità capillare nella malattia di Bouillaid.) ZANGARA, A., SICCARDI, A., and PICCIONI, A. (1959). *Reumatismo*, **11**, 191. 3 figs, 32 refs.

Recent experimental findings have underlined the intimate anatomical and functional interrelationship between capillaries and connective tissue, which are of common embryological origin, and have also thrown light on the characteristic association of vascular lesions with lesions of the connective tissue in acute rheumatism and other diseases. Many authors are of the opinion that the systemic, structural, and functional damage produced in the capillaries by the rheumatic diseases is responsible in whole or in part for their pathogenesis. Cortisone, corticotrophin (ACTH), and the salicylates generally reduce capillary permeability in these diseases in parallel with their production of clinical improvement. Chlorpromazine also reduces capillary permeability, but the effect of phenylbutazone on the vessels is doubtful.

The present authors, working at the Medical Clinic of the University of Genoa and the Civil Hospital, San Remo, have studied the behaviour of capillary permeability during the treatment of cases of rheumatic fever with prednisone and dexamethasone. Clinically, dexamethasone showed a marked superiority. Among the various available methods of evaluating capillary permeability, the Landis test was preferred by the authors for its technical simplicity and dependability. This test confirmed the superiority of dexamethasone over prednisone, the latter producing no marked reduction in capillary permeability, whereas the former, in doses 6 to 8 times smaller, had a prompt and easily demonstrable effect. This effect may, however, have been enhanced by previous treatment with prednisone.

Robert E. Lister.

Nature of Scarlatinal Arthritis. CREA, M. A., and MORTIMER, E. A. (1959). *Pediatrics*, **23**, 879. 15 refs.

During the period 1938-57 about 6,000 patients with scarlet fever were admitted to the City Hospital, Cleveland, Ohio. Among these, nineteen were recorded as having concomitant arthritis or rheumatic fever (excluding septic arthritis and arthritis secondary to serum sickness) during the first week of the illness, eighteen of whom were followed up 1 to 20 years later to determine the incidence of valvular heart disease. There were twelve females and six males in the series, only three of whom had been admitted since 1946. One patient (a male aged 4 years) had died from acute rheumatic pancarditis one month after contracting scarlet fever.

Of the survivors, thirteen were examined by the authors and four by their own physician. In eight cases (44 per cent.) there were no signs of valvular heart disease and no history of acute rheumatism since the original episode. In only four patients (three females, one male) were heart murmurs of an organic character—aortic and mitral diastolic, apical presystolic and systolic—noted at the time of follow-up. Of the remainder, however, one patient had developed signs of rheumatic pancarditis during the original illness, two had had subsequent

attacks of rheumatic fever or chorea, and in the remaining two the original arthritis had been recurrent or unduly persistent. It is therefore concluded that in ten (56 per cent.) of the eighteen cases there was evidence that the original arthritis was, or may have been, a manifestation of acute rheumatism.

The authors review previous work on this complication and offer two possible explanations for the simultaneous occurrence of scarlet fever and rheumatic fever:

(1) That the patient has experienced a different streptococcal infection one to 5 weeks before that responsible for scarlet fever; or, more likely:

(2) That scarlatinal arthritis represents true rheumatic fever developing, after an unusually short latent period, as a result of infection with the scarlatinal streptococcus in persons predisposed to rheumatism.

They suggest that the present criteria for the diagnosis of rheumatic fever are too rigid, and emphasize the need for a specific diagnostic test. *I. M. Librach.*

Secretion of Blood-group Substances in Rheumatic Fever —a Genetic Requirement for Susceptibility. GLYNN, A. A., GLYNN, L. E., and HOLBOROW, E. J. (1959). *Brit. med. J.*, **2**, 266. 17 refs.

The presence of the ABH and Le^a blood-group substances in the saliva of healthy schoolchildren and of cases of rheumatic fever has been studied. By the ulex test 22·9 per cent. of 669 healthy schoolchildren were non-secretors, the comparable figure for 553 rheumatic fever cases was 28·9 per cent. Positive results with a precipitation test on the saliva with a rabbit anti-Le^a serum were obtained in 21·2 per cent. of 1,129 healthy schoolchildren and in 27·5 per cent. of 611 cases of rheumatic fever. These two differences, significant at the 2 per cent. and 1 per cent. level respectively, would be expected if rheumatic fever could develop only in those individuals who are homozygous or heterozygous for the non-secretor gene. On the basis of this hypothesis we have shown that the incidence of rheumatic fever in the parents and sibs of patients with this disease should not, on hereditary grounds, be more than 13 and 16 per cent. greater respectively than in the general population.—[*Authors' summary.*]

Serum Inhibition of Streptococcal Diphosphopyridine Nucleotidase in Uncomplicated Streptococcal Pharyngitis and in Rheumatic Fever. BERNHARD, G. C., and STOLLERMAN, G. H. (1959). *J. clin. Invest.*, **38**, 1942. 1 fig., 18 refs.

Skin Reactions with Distreptase as One of the Diagnostic Methods in Rheumatic Fever. (Odczyny skórne z distreptazą jako jedna z metod rozpoznawczych w chorobie reumatycznej.) LICHT, E., WYSOCKA-IGNATOWSKA, Z., and NOWOTARSKA, T. (1959). *Pediat. pol.*, **34**, 1147. 4 refs.

Trials of the Evaluation of the Influence of Rheumatic Fever on the Respiratory System in Children. (Próby oceny wpływu choroby reumatycznej na narząd oddychania u dzieci.) CHRAPOWICKI, T., and SZEWCZYKOWSKA, M. (1959). *Pediat. pol.*, **34**, 919. 6 figs, 5 refs.

Observations on the Prevention of New Attacks of Rheumatic Fever. (Spostrzeżenia nad zapobieganiem nowym rzutom choroby reumatycznej.) JARZĘBSKA, D., LEŚKIEWICZ, W., and SUFFCZYSŃKA, M. (1959). *Pediat. pol.*, **34**, 931. 4 refs.

Prevention of Rheumatic Fever Recurrence. BERMAN, B. B. (1959). *Illinois med. J.*, **116**, 255.

Early Transient Mid-Diastolic Murmur in Rheumatic Fever. WERBIN, B. Z. (1959). *Amer. J. Cardiol.*, **4**, 356. 2 figs, 6 refs.

Hormone Therapy of Rheumatic Fever. (Hormonlání Terapie revmatické Horečky.) HAUER, J. (1959). *Čas. Lék. čes.*, **98**, 1432. 49 refs.

Behaviour of 17-Ketosteroids in Urine during the Treatment of Rheumatic Fever with Sodium Salicylate. (Zachowanie się 17-ketosteroidow w moczu w czasie leczenia choroby reumatycznej salicylanem sodu.) MORAWSKA, Z., and PUZIEWICZOWA, I. (1959). *Pediat. pol.*, **34**, 1047. 9 refs.

Significance of the Trafuril Test, with Special Reference to Atopy and Rheumatic Fever. A Capillaroscopic Study. ROVENSKÝ, J., and PREIS, A. (1959). *Ann. paediat.* (*Basel*), **193**, 289. 6 figs, 46 refs.

National Attack on Rheumatic Fever. MCGUINNESS, A. C. (1959). *Publ. Hlth Rep.* (*Wash.*), **74**, 870.

Results of Control Examinations of Convalescents Several Years after an Acute Attack of Rheumatic Fever. (Výsledky kontrol v ústřední vojenské nemocnici v praze léčených rekonvalescent ů po revmatické horečce po létech od akutní ataky.) HAUER, J. (1959). *Čas. Lék. čes.*, **98**, 1435. 27 refs.

Influence of Prednisolone and Dexamethasone on the Serum Proteins in Patients with Rheumatic Carditis. (Influenza del prednisolone e del desametasone sulle proteine seriche in infermi affetti da cardite reumatica.) VILLANO, F., ODOARDI, G. B., and RAMBALDI, M. (1959). *Rif. med.*, **73**, 1187. 33 refs.

Rheumatic Fever and Antistreptolysin-O Titre. JULKUNEN, H., and KAIPAINEN, W. J. (1959). *Ann. Med. intern. Fenn.*, **48**, 81. 6 refs.

Low-cost Penicillin for Prevention of Rheumatic Fever. LICHTY, J. A., and SEIKEL, A. (1959). *Rocky Mtn med. J.*, **56**, 61. 10 refs.

Chronic Articular Rheumatism (Rheumatoid Arthritis)

Critical Study of the "Rheumatoid Lung Syndrome". (Zur Kritik des "rheumatoid lung syndrom".) HOHNBERG, H. (1959). *Z. ges. inn. Med.*, **14**, 439. 17 refs.

The author notes that German-speaking authors have made little reference to the "rheumatoid lung" syndrome, a condition first described by Ellman and Ball in 1948 (*Brit. med. J.*, 1948, **2**, 816; *Abstr. Wld Med.*, 1949, **6**, 101) and later more fully discussed by Ellman and Cudkowicz (*Thorax*, 1954, **9**, 46; *Abstr. Wld Med.*, 1954, **16**, 236) and many others. The syndrome comprises an active polyarthritis, with cough, fever, shortness of breath, and often leucocytosis. Radiologically, the lungs show net-like shadows which occasionally coalesce. Post mortem the arterioles and capillaries of the pleura and the intrapulmonary connective tissue are seen to be the primary site of attack. Other British workers, however, have reviewed a large number of cases of rheumatoid arthritis and have concluded that the pulmonary changes are not specific [for example, Aronoff and Bywaters (*Brit. med. J.*, 1955, **2**, 228; *Abstr. Wld Med.*, 1956, **19**, 229)].

The present author, working at the Medical Academy, Magdeburg, has reviewed 109 cases of rheumatoid arthritis. In nine of these there was no clinical evidence of any lung complications. The other hundred were examined radiologically and a number were found to be suffering from emphysema, pneumonia, or other pulmonary lesions, but there were no changes which could be attributed to "rheumatoid lung". In two of these patients who died—one of lymphatic leukaemia and the other of a septic nephritis—no significant lung changes were found at necropsy. On the basis of this study, therefore, the author also concludes that any lung changes present in patients with rheumatoid arthritis are not specific for that disease, but may be associated with any of the other collagen diseases. *D. Preiskel.*

Triamcinolone in the Treatment of Rheumatoid Arthritis. THOMPSON, M. (1959). *Brit. med. J.*, **1**, 1259. 13 refs.

A study of the comparative efficacy of triamcinolone and prednisolone in the treatment of fifteen patients with rheumatoid arthritis and one patient with ankylosing spondylitis is reported from the Royal Victoria Infirmary, Newcastle-upon-Tyne. All the patients received treatment with prednisolone and triamcinolone successively, the ratio of dosage being 5 : 4 by weight; the daily maintenance dosage of prednisolone ranged from 7·5 to 20 mg. The duration of treatment with triamcinolone varied from 2 to 26 weeks. Response to treatment was judged on the basis of the patient's own assessment of pain and the duration of morning stiffness as well as on the physician's assessment of functional capacity and disease activity. At regular intervals the strength of grip was measured and the erythrocyte sedimentation rate (E.S.R.) was estimated by Westergren's method. In seven patients capillary resistance was measured by the method of Potter and Wigzell.

It was found that in respect of functional capacity, disease activity, strength of grip, and the patient's own assessment the difference between the two drugs was very small. The E.S.R., however, was lower during triamcinolone therapy in eleven cases, equal in two and lower during prednisolone therapy in three. Serial measurements of capillary resistance did not show any important difference. All except two patients lost weight while receiving triamcinolone. Diastolic blood pressure was 90 mm. Hg or more during prednisolone therapy in nine patients, and in all nine there was a fall in blood pressure during administration of triamcinolone. Three patients who had dyspepsia while taking prednisolone experienced an increase in the severity of the symptoms when triamcinolone was given. Dyspepsia occurred for the first time in four patients during triamcinolone therapy; one of these patients had a haematemesis. Lesions of subcutaneous ecchymoses developed in two cases during prednisolone administration, but regressed when triamcinolone was substituted. Two patients who were euphoric on prednisolone became calmer on triamcinolone. No change was observed in the acne, moon face, or hirsuties present in six patients when prednisolone was replaced by triamcinolone. *C. E. Quin.*

Investigation of the Presence of a Common Antigenic Factor in Certain Cocci and the Relationship with Rheumatoid Arthritis. [In English.] BEEUWKES, H., BULSMA, A., and MENDES DE LEON, D. E. (1959). *Acta rheum. scand.*, **5**, 101. 3 refs.

In a previous paper (*Acta med. scand.*, 1957, **157**, 119; *Abstr. Wld Med.*, 1957, **22**, 218) the authors reported that tanned erythrocytes coated with extracts of Group-A haemolytic streptococci were agglutinated by sera from patients with rheumatoid arthritis. In the present work, reported from St. Joseph Hospital, Heerlan, and St. Annadal Hospital, Maastricht, Netherlands, they first investigated the effect of using acetamide extracts of various other micro-organisms instead. Extracts of Gram-negative bacilli and pneumococci gave no reactions with serum from a case of rheumatoid arthritis which gave a positive result in the original test, but extracts of β-haemolytic streptococci and most staphylococcal strains gave positive reactions with this serum.

Extracts were also made from strains of α-haemolytic streptococci isolated from the throats of twenty patients with rheumatoid arthritis and of thirty normal subjects and these were used to coat tanned erythrocytes. Sera from these individuals were then tested against cells coated with extracts of autologous cocci and against cells coated with a standard Group-A streptococcal extract. Of the sera from normal subjects, none gave positive autologous reactions and four agglutinated the standard extract. Of the rheumatoid arthritis sera, three gave positive autologous reactions and eleven agglutinated the standard extract. This work, these authors claim, suggests that certain people produce antibodies against their own throat flora which play a part in the pathogenesis of rheumatoid arthritis. *E. J. Holborow.*

Present State of Adrenocortical Hormone Therapy in Rheumatoid Arthritis. (État actuel de l'hormonothérapie corticosurrénale des rhumatismes inflammatoires chroniques.) COSTE, F., DELBARRE, F., and CAYLA, J. (1959). *Presse méd.*, **67**, 1177. 1 ref.

In this paper from the National Institute of Hygiene and the Hôpital Cochin, Paris, the authors review in detail the results of long-term steroid therapy in one hundred patients, of whom six had ankylosing spondylitis and the remainder rheumatoid arthritis. The mean duration of treatment was 3 years, with a range of 1 to over 7 years in individual cases. All the patients are now treated with prednisone, although earlier one-third had received cortisone, hydrocortisone, or ACTH. The maintenance dose of prednisone was usually 10 mg. or even less; the authors now consider it preferable to start with a dose of this order rather than one of 15 mg. or more, and then reducing. So far as possible aspirin, phenylbutazone, and chloroquine were also given to help to limit the dose of steroid required. However, the value of aspirin in this respect was slight and the authors are "far from confirming" the conclusion reached in a British survey [no reference given] that in the long run aspirin is as valuable as, if not superior to, hormone therapy. The other drugs mentioned were often limited in use by gastric intolerance; however, when tolerance is good, chloroquine and hydroxychloroquine are valuable, and in five patients the use of these drugs ultimately enabled steroid therapy to be withdrawn. ACTH was used mainly to cover withdrawal of steroids, and the authors deprecate its use for intermittent "boosting" of the adrenal cortex.

The patients with rheumatoid arthritis were classified in four grades of severity. At the final assessment 63 per cent. showed an improvement in grade during treatment, 30 per cent. remained static, and 7 per cent. deteriorated. [There is no mention of a control group.] Before the start of steroid treatment ten of the 94 patients were classified as Grade 1 (with little restriction of physical activity); ultimately 44 could be placed in this Grade, and a further five had lost all signs of rheumatoid arthritis. Of the six patients with ankylosing spondylitis three showed improvement, mainly in peripheral joints. In regard to side-effects, gastro-intestinal symptoms were common (36 per cent., although proven ulcer occurred in only 6 per cent.; these symptoms were not related to the dosage of steroid, but their incidence was twice as high in those with a past history of dyspepsia. Osteoporosis occurred in 16 per cent., resulting in vertebral fractures in eight and fractured neck of femur in two patients. Here the danger was greatest with higher dosage (over 15 mg. daily), length of treatment, degree of immobility, and in women over 60 years of age. Of the nine deaths in the series, two were attributable to steroid therapy (gastric haemorrhage and miliary tuberculosis respectively), and three probably so (adrenal insufficiency in two cases and amyloid disease in one). The remaining four deaths were due to other causes, although possibly aggravated by sudden withdrawal of steroid therapy.

In summing up, the authors stress the need for proper precautions in order to achieve the best and very real advantages of steroid therapy. They warn particularly against the dangers of adrenal inhibition and against sudden withdrawal of steroids; they are reserved in their attitude to the new successor drugs to prednisone.

J. A. Cosh.

Steroid Therapy and Vascular Lesions in Rheumatoid Arthritis. JOHNSON, R. L., SMYTH, C. J., HOLT, G. W., LUBCHENCO, A., and VALENTINE, E. (1959). *Arthr. and Rheum.*, **2**, 224. 10 figs, bibliography.

The authors of this paper from the University of Colorado School of Medicine, Denver, describe the clinical and necropsy findings in three patients suffering from rheumatoid arthritis in whom diffuse arteritis developed. The patients had been receiving steroid therapy for 15 months to 3 years before the onset of symptoms of arteritis and all had hypercortisonism. The first indication of the presence of arteritis was the development of symptoms and signs of polyneuritis; the patients were febrile.

Gangrene of the finger tips and around the ankles developed in one patient; later, signs and symptoms appeared suggesting arterial occlusion in the heart or brain. A leucocytosis was present, the leucocyte count varying between 18,000 and 53,000 per c.mm. Microscopical examination of tissue removed at necropsy revealed polyarteritis affecting the majority of sections from the visceral and musculo-skeletal systems. The vascular lesions resembled those of polyarteritis nodosa.

Adrenocortical steroids were given in the treatment of 138 patients with rheumatoid arthritis attending the University of Colorado Medical Center in 1957. Of these, fourteen developed peripheral neuropathy—9 while receiving steroids and five over a period of 1 to 5 months after steroid therapy had been discontinued. Before the onset of peripheral neuropathy thirteen patients had received prednisone in a dosage of 10 to 20 mg. daily and one patient had received cortisone. The patients complained of pain and numbness and tingling in the hands and feet. Examination revealed sensory loss of glove and stocking type, weakness of peripheral muscles, and decreased tendon reflexes. Purpuric lesions occurred in ten of the fourteen cases. The authors consider that the peripheral neuropathy noted in these fourteen cases was due to arteritis affecting the nutrient arteries of peripheral nerves. After reviewing the literature they point out that although arteritis is known to occur in patients with rheumatoid arthritis who have never received steroids, the incidence of this complication has increased since the introduction of steroid therapy.

C. E. Quin.

Relation of the Rheumatoid Factor Content of Serum to Clinical Neurovascular Manifestations of Rheumatoid Arthritis. EPSTEIN, W. V., and ENGLEMAN, E. P. (1959). *Arthr. and Rheum.*, **2**, 250. 5 figs, 21 refs.

This report describes nine patients with rheumatoid arthritis who had in common severe deforming disease, subcutaneous nodules, large amounts of circulating rheumatoid factor and significant ischaemic skin changes

and/or peripheral neuropathy. All nine had been treated with adrenocortical steroids for periods ranging from 1½ to 5 years. The incidence of subcutaneous nodules and the magnitude of the F II haemagglutination titre in these patients are significantly different from those found in a population of patients with rheumatoid arthritis. No direct correlation was found between absolute end-point titres and the clinical neurovascular complications. The association of rheumatoid arthritis of Stage III or IV, subcutaneous nodules and the presence of large amounts of rheumatoid factor in the serum may constitute a relative contraindication to the use of adrenocortical steroid therapy.—[*Authors' summary.*]

Surgical Rehabilitation of the Arthritic Hand. FLATT, A. E. (1959). *Arthr. and Rheum.*, **2**, 278. 1 fig., 11 refs.

This article from the department of Orthopaedic Surgery of the State University of Iowa is a review of current thought upon some aspects of hand surgery in rheumatoid arthritis. In the early stages the disease may be confined to the sheaths of tendons, and complete excision of the involved sheath sometimes appears to control the progress of the disease. Tendon ruptures in rheumatoid arthritis are becoming increasingly recognized as a cause of deformity. This may be due to frictional attrition of the tendon over a rough spur of bone in the affected joint, or more commonly, to degeneration of the tendon with spontaneous rupture. This is a common cause of finger deformity, and any of the fibres of the extensor or flexor tendons may be involved. Prompt recognition of the condition, and surgical treatment by tendon transfer or grafting is imperative if function is to be retained. The deformity of the fingers is often increased by contracture of the intrinsic muscles, and may be remedied by intrinsic release, or by extensor tenodesis.

Where the joint involvement is marked, either arthrodesis of the affected joint, or occasionally arthroplasty, can achieve a considerable increase in the function of the whole hand. In the proximal interphalangeal joint, the retention of movement may be of great importance, and the author describes a prosthesis which is being developed to permit a satisfactory arthroplasty of this joint. Most surgical procedures can be carried out with safety when the disease is active, and a plea is made for the earlier consideration of surgery in these patients. *Peter Ring.*

Clinical and Pathological Study of Polyneuritis arising during the Course of Rheumatoid Arthritis. (Étude anatomo-clinique des multinévrites au cours des polyarthrites chroniques évolutives.) GRAVELEAU, J., DEMAISON, F., and MORIN, M. (1959). *Sem. Hôp. Paris*, **35**, 2080. 7 figs, 48 refs.

In view of the rarity of neurological complications in rheumatoid arthritis the authors report two further cases seen at the Hôpital Foch, Suresnes, Paris, in which polyneuritis due to periarteritis nodosa was present as a complication of rheumatoid arthritis. Both occurred in women aged 64 in whom the rheumatoid disease had existed for 11 and 4 years respectively. Both had received courses of gold therapy in the past and more recently treatment with prednisone. Fever accompanied by generalized pain was noted in both cases. There was a leucocytosis of 15,000 per c.mm., with a preponderance of polymorphonuclear leucocytes, in one case and of 18,960 per c.mm. in the other. The neurological signs included paralysis or paresis of the extremities with absent tendon jerks, and hypoaesthesia of the hands and feet; in addition there was exquisite tenderness on compressing the muscles. Muscle biopsy examination performed in both cases demonstrated periarteritis nodosa affecting the arterioles. One patient died and at necropsy widespread foci of periarteritis were found. The other recovered, but the neurological signs showed little change and gangrene developed in one toe.

The authors present an extensive review of the literature in which previous similar cases have been reported. In most the signs and symptoms were as described above, and a history of gold, copper, or steroid therapy was common, particularly the last in the more recent cases. Neurological signs, usually symmetrical, generally affect the extremities, but rarely the distribution of the cranial nerves. *Post mortem*, the arterial lesions are found to be widespread, and have been demonstrated in the heart muscle and valves, spleen, intestine, kidney, and the nutrient arteries of peripheral nerves. The treatment of such cases is extremely difficult, involving as it does the cessation of steroid therapy with the risk of serious withdrawal symptoms. These patients have often been receiving high doses of steroids and their too rapid withdrawal has been known gravely to increase the extent of the paralysis. In the authors' opinion the treatment of these neuropathies can only be prophylactic, meaning thereby that steroids should be prescribed only in exceptional cases of rheumatoid arthritis and then in low dosage. *William Hughes.*

Comparative Effects of Phenylbutazone and G27202 (Metabolite I) in Patients with Rheumatoid Arthritis: an Assessment of Methods for Antirheumatic Drug Evaluation. VAUGHN, P. P., HOWELL, D. S., and KIEM, I. M. (1959). *Arthr. and Rheum.*, **2**, 212. 5 figs, 13 refs.

For various periods during an investigation lasting 12 weeks, 24 adult patients with rheumatoid arthritis were given aspirin, a placebo, phenylbutazone, and metabolite I, a derivative of phenylbutazone. The last two drugs were given in doses of 800 mg. on the first day and 600 mg. on the second day; subsequently the dose was maintained at 400 mg. daily. Observations were controlled by administering the drugs in the form of a white powder in gelatin capsules of identical appearance. Throughout treatment special note was made of any changes in joint swelling, degree of tenderness, pain, morning stiffness, fatigue, speed of walking, and grip.

Apart from salt and water retention during the early phases of treatment there were no important side-effects from administration of metabolite I. The response to this drug was at least equal to the response obtained with phenylbutazone. During metabolite I therapy there was highly significant improvement in grip and in the duration

of morning stiffness. On the other hand, equivocal results were obtained with completely objective measurements such as the erythrocyte sedimentation rate and joint circumference. Altogether an excellent or a good response was obtained in twelve cases.

A. Garland.

Corticosteroid Therapy in Rheumatoid Arthritis: Comparative Study of Effects of Prednisone and Prednisolone, Methylprednisolone, Triamcinolone, and Dexamethasone. NEUSTADT, D. H. (1959). *J. Amer. med. Ass.*, **170**, 1253. 15 refs.

At the Arthritis Clinic of the University of Louisville 65 patients (39 female and 26 male) with rheumatoid arthritis were treated with prednisolone or prednisone, methylprednisolone, triamcinolone, or dexamethasone. Since no difference has been reported in the literature between prednisone and prednisolone, these two preparations are grouped together as "prednisteroids". The patients' ages ranged from 23 to 71 years and the average duration of the disease was 7 years. Each patient was classified in respect of severity of the disease and functional disorder according to the criteria of the American Rheumatism Association, 31 patients being in Stages 3 and 4 (moderately advanced and advanced). None of the patients had received antimalarials or gold therapy within one year of starting treatment with corticosteroids, although all had received salicylates and "basic therapy". A clinical evaluation of each patient was performed "at regular and frequent intervals". Certain laboratory studies were carried out periodically, including estimation of the haemoglobin level and haematocrit, total and differential leucocyte counts, erythrocyte sedimentation rate, total plasma protein and albumin and globulin levels, and urinary sugar and albumin content.

In 48 cases prednisteroids were given for an average period of 2 years. Methylprednisolone was given to 39 patients, of whom 32 had previously received long-term prednisteroid therapy, and 25 received triamcinolone before or after the methylprednisolone, while in seven cases methylprednisolone was the only corticosteroid given. Triamcinolone was given to 38 patients, of whom 31 had received prednisteroids and 25 were given methylprednisolone either before or after the triamcinolone, triamcinolone being the only corticosteroid given in seven cases. A firm maintenance dose of each corticosteroid was established before another was substituted. Patients served as their own controls without the administration of placebos as soon as the early part of the study was finished. This method of comparison was preferred to the double-blind method, mainly because of the dangers of interrupting corticosteroid treatment. Altogether 25 patients received prednisteroids, triamcinolone, and methylprednisolone for sufficiently long periods to allow comparative analysis of the results. The remaining forty patients did not receive all these corticosteroids and are therefore not included in the analysis. On the other hand forty patients were later given dexamethasone, enabling a preliminary comparison of the effects of this and other corticosteroids to be made.

Comparable antirheumatic effects were obtained with all compounds in the majority of cases. The average daily maintenance doses were: prednisteroids, 11·4 mg.; triamcinolone, 7·8 mg.; methylprednisolone, 8·12 mg.; and dexamethasone, 1·4 mg. The laboratory investigations revealed no consistent difference between the various corticosteroids except that glycosuria and an increase in the blood sugar level occurred more often with the prednisteroids than with the other preparations. The side-effects occurring in the 25 patients who received adequate treatment with prednisteroids, methylprednisolone, and triamcinolone are listed. The incidence of the expected manifestations of hypercortisonism and of peptic ulcer and other gastro-intestinal symptoms was similar with all compounds. Emotional disturbances, oedema, and glycosuria occurred most often with the prednisteroids and ecchymotic and purpuric skin manifestations with methylprednisolone. Two "new" side-effects are reported as occurring almost exclusively with triamcinolone, namely "hot flushes", erythema of the face, and increased perspiration and, more serious, muscle weakness accompanied by loss of weight, which occurred in about 24 per cent. of patients receiving this steroid. In contrast, dexamethasone had a remarkable appetite-stimulating effect and produced a striking gain of weight.

None of the steroids was outstandingly superior to the others in clinical effect and freedom from side-effects. The author concludes that methylprednisolone is probably the steroid of choice for initial treatment, but dexamethasone may prove useful for the early treatment of the underweight patient with rheumatoid arthritis.

J. Warwick Buckler.

Radiological Changes in the Bones in Juvenile Rheumatoid Arthritis and Their Reversibility. (Über röntgenologische Knochenveränderungen bei primärchronischer Arthritis im Kindesalter und ihre Rückbildungsfähigkeit.) SPEISS, H. (1959). *Mschr. Kinderheilk.*, **107**, 317. 12 figs, 20 refs.

This study of three children with Still's disease, in each of whom it took a different course, is reported from the University Paediatric Clinic, Göttingen. Although the disorder is generalized, the bones consistently tend to become demineralized and osteoporotic, and this tendency is believed to be aggravated by the modern use of ACTH (corticotrophin) and steroids, which do not necessarily arrest the disease process. The administration of vitamin D helps to counteract the tendency to demineralization, but unfortunately it also diminishes the beneficial effects of the hormones. For this reason the author suggests that the vitamin should not be given unless osteoporosis is marked; if it is given its administration should be accompanied by prompt reduction in the dosage of steroids, or they may be given intermittently, or better still completely omitted. Radiologically, in all three of the author's cases some of the changes in the bones were subsequently reversed, but it is stressed that orthopaedic measures and long-term physiotherapy form an integral and essential part of the treatment. [There is no indication of the dosage of vitamin D or the type of preparation employed.]

D. Preiskel.

Rheumatic-like Nodules occurring in Non-rheumatic Children. BEATTY, E. C., JR. (1959). *A.M.A. Arch. Path.*, **68**, 154. 4 figs, 13 refs.

Over a recent 10-year period at the Children's Hospital, Denver, Colorado, subcutaneous nodules were removed from nine children, aged 11 days to 9 years, in whom there was no evidence of rheumatic disease. The nodules were found on the limbs or on the scalp. Histological examination revealed foci of necrosis surrounded by fibroblasts and histiocytes, with scattered chronic inflammatory cells. The author concludes that the similarity of these lesions to rheumatic nodules is noteworthy.

[The photomicrographs reproduced show necrosis and a cellular "palisade"; these features are very rarely seen in rheumatoid arthritis in children (*see* Bywaters and others, *Ann. rheum. Dis.*, 1958, **17**, 278; *Abstr. Wld Med.*, 1959, **25**, 153) or in rheumatic fever.] *G. Loewi.*

Correlative Study of the Erythrokinetics and Disturbances in Iron Metabolism Associated with the Anaemia of Rheumatoid Arthritis. WEINSTEIN, I. M. (1959). *Blood*, **14**, 950. 7 figs, 32 refs.

A study is reported from the University of California Medical Center, Los Angeles, of erythrocyte production and destruction and disturbances in iron metabolism (using histological, serological and radio-isotope techniques) in eighteen patients with active rheumatoid arthritis, of whom thirteen had typical rheumatoid arthritis, but five had additional complications; for instance two had "malignant" rheumatoid arthritis, two gave a positive L.E.-cell test reaction (one of these also having splenomegaly), and one had splenomegaly, leucopenia, and anaemia. The patients in the atypical group were in general more severely ill.

In nine of the thirteen patients with typical rheumatoid arthritis and in four of the five atypical patients the erythrocyte volume was abnormally low. Most of these patients also had a low serum iron level, with rapid disappearance of radioactive iron (^{59}Fe) from the plasma and an increased rate of turnover of iron. However, the utilization of ^{59}Fe by newly-formed erythrocytes was very good in both the typical and atypical groups, only three of the thirteen patients in the typical group showing definitely abnormal utilization of ^{59}Fe. Histological examination of the bone marrow in these patients failed to reveal any significant evidence of impaired erythropoiesis. Six of the thirteen patients in the typical group and four of the five in the atypical group showed abnormal erythrocyte survival times, but it is emphasized that this shortening of the life span cannot in itself account for the development of anaemia, since it should be compensated for by an uninhibited bone marrow. Studies of the distribution of ^{59}Fe and radioactive chromium (^{51}Cr) showed that in the majority of these patients this was normal. In nine of the eighteen patients the plasma volume was greater than normal, and although such an increase would not account entirely for the anaemia it would suggest that in some instances the so-called anaemia of uncomplicated rheumatoid arthritis may be due to dilution of the plasma volume. There appeared to be no relationship between the lowering of the serum iron level and the anaemia in these patients with rheumatoid arthritis. Estimation of the degree of anaemia by the haematocrit value or the actual determination of erythrocyte volume suggested that the absorption of iron in these patients was not significantly different from that in normal subjects, and it appeared that the low serum iron levels did not stimulate an increased absorption of the iron from the gastro-intestinal tract, as occurs in straightforward iron-deficiency anaemia. It has been suggested that in rheumatoid arthritis and in similar diseases there may be a defect in the mobilization of iron from the reticulo-endothelial system, but this could not be confirmed in the present study. The author concludes that severe anaemia associated with rheumatoid arthritis suggests the presence of complications such as a superimposed iron deficiency, malignant rheumatoid disease, hypersplenism, or an underlying diagnosis of disseminated lupus erythromatosus. *R. F. Jennison.*

Value of Functional Radiography of the Joints between the First and Second Vertebrae, with Special Reference to Rheumatoid Arthritis and Soft-tissue Injuries. (Der Wert der funktionellen Röntgen-Untersuchung der Gelenke zweschen erstem und zweitem Halswirbel.) DJIAN, A., and ZINN, W. (1959). *Z. Rheumaforsch.*, **18**, 279. 8 figs, 15 refs.

Fracture of the Cervical Spine in Patients with Rheumatoid Arthritis. LEMMEN, L. J., and LAING, P. G. (1959). *J. Neurosurg.*, **16**, 542. 5 figs, 8 refs.

Fatal Fulminating Necrotizing Vasculitis in Steroid-Treated Rheumatoid Arthritis. BORMAN, M. C., GARVEY, J., WELSH, E. C., KOENIG, R. R., and POLCYN, B. M. (1959). *Wis. med. J.*, **58**, 557. 4 figs, 5 refs.

Crico-arytenoid Joint. A Diarthrodial Articulation Subject to Rheumatoid Arthritic Involvement. POLISAR, I. A. (1959). *Laryngoscope (St. Louis)* **69**, 1129. 9 figs, bibl.

Serological Tests in Differential Diagnosis and Control of Rheumatoid Arthritis. (Seroreaktioner vid diagnostik och kontroll av reumatoid arthrit.) SVARTZ, N. (1959). *Nord. Med.*, **62**, 1543. 7 figs, 24 refs.

Some Psychiatric Aspects of Fifty Cases of Rheumatoid Arthritis. (Algunos aspectos psiquiatricos en 50 casos de artritis reumatoidea.) SÁNCHEZ, V., DAVANZO, H., and BUVINIC, M. (1959). *Arch. argent. Reum.*, **22**, 35.

Comparative Study of Certain Metabolic and Hormonal Effects of Triamcinolone, 6-Methyl-Prednisolone, and Prednisone in Cases of Rheumatoid Arthritis. (Estudio comparativo de algunos efectos metabolicos y hormonales de la triamcinolona la 6-metilprednisolona y la prednisona en enfernos de artritis reumatoidea.) RAVEST, F. V., CRUZ, R. A., and VARGAS, A. J. (1959). *Arch. argent. Reum.*, **22**, 56. 4 figs, 10 refs.

Chloroquine in the Treatment of Rheumatoid Arthritis. (Chloroquinbehandlung beim primär chronischen Rheumatismus.) MERKEL, G. (1959). *Z. ges. inn. Med.*, **14**, 762. 10 refs.

Value of the Intradermal Congo Red Test in Rheumatoid Arthritis. CSÁSZÁR, G. (1959). *Acta rheum. scand.*, **5**, 229. 2 figs, 23 refs.

Research on the Treatment of Rheumatoid Arthritis with Combined Steroids. I. Triamcinolone and Prednisolone. (Ricerche sulla cura dell'artrite reumatoide con associazioni steroidee. I. Associazione triamcinolone e prednisolone.) ROBECCHI, A., and DI VITTORIO, S. (1959). *Reumatismo*, **11**, 249.

Treatment of Rheumatoid Arthritis with Resochin (Chloroquine). (Zur Resochinbehandlung der primär chronischen Polyarthritis rheumatica.) GÜNTHER, R. (1959). *Med. Klin.*, **54**, 2073. 2 figs, 12 refs.

Radiological Appearances in the Small Intestine in the Collagen Diseases. (a) The Small Intestines in Rheumatoid Arthritis. (Aspetti radiologici del tenue nelle collagenopatie. (*a*) Il tenue nell'artrite reumatoide.) VITERBO, F., ALBANO, O., and CAVALLO, A. (1959). *Arch. ital. Mal. Appar. dig.*, **26**, 205. 13 figs, 12 refs.

***In vitro* Absorption of Serotonin by Thrombocytes of Rheumatoid Arthritic and Non-Arthritic Individuals.** KERBY, G. P., and TAYLOR, S. M. (1959). *Proc. Soc. exp. Biol. (N.Y.)*, **102**, 45.

6-α-Methyl Prednisolone in the Treatment of Rheumatoid Arthritis. THOMPSON, M. (1959). *Ann. phys. Med.*, **5**, 122. 17 refs.

Rheumatoid Cysts of the Calf. BEATTY, D. C. (1959). *Proc. roy. Soc. Med.*, **52**, 1106. 5 figs, 6 refs.

Experience in the Treatment of Rheumatoid Arthritis with Chloroquine. (Erfahrugen über die Chloroquinbehandlung bei primär-chronischer Polyarthritis.) SCHIMANSKI, J., and SÜDHOF, H. (1959). *Z. Rheumaforsch.*, **18**, 459. 23 refs.

Question of the Origin of Muscular Atrophy in Rheumatoid Arthritis. (Zur Frage der Entstehung der Muskelatrophie bei chronischer Polyarthritis.) GÁSPÁRDY, G., KOVÁCS, L., SIMON, M., and VIDA, M. (1959). *Z. Rheumaforsch.*, **18**, 455. 21 refs.

(Osteo-Arthritis)

Spontaneous Haemarthrosis in Osteo-Arthritis of Knee. A Report of Five Cases. WILSON, J. N. (1959). *Brit. med. J.*, **1**, 1327. 1 fig., 2 refs.

Extensive haemarthrosis unrelated to severe trauma or blood dyscrasia has hitherto been considered rare. Over a recent 2-year period the author of this paper from the Institute of Orthopaedics, London, has collected details of five cases of spontaneous haemarthrosis of the knee with osteo-arthritis. In three of the cases there had been more than one episode of haemarthrosis. The onset of painful, tense swelling of the knee was very rapid, and in all cases trauma was minimal or absent. It is suggested that the haemarthrosis is due to nipping of synovial tags, perhaps in the vascular fringe round a deformed patella. Aspiration of the joint should be carried out as soon as possible, particularly if the haemarthrosis is large; disability should not then be prolonged.

J. N. Agate.

Preliminary Results obtained with a New Sulphonamide-Analgesic Combination in the Treatment of Osteo-Arthritis. (Primeros resultados obtenidos con una nueva asociación azufre-analgésicos en el tratamiento de las artrosis.) BARCELO, P., and SANTAMARIA, A. (1959). *Rev. esp. Reum.*, **8**, 38.

***X*-Ray Treatment of Osteo-Arthritis of the Spine.** LOBO, P. S. (1959). *Indian J. Radiol.*, **13**, 120.

Surgical Approach to Osteo-Arthritis. FRENCH, P. (1959). *Brit. J. clin. Pract.*, **13**, 622.

Osteochondromatosis and Osteo-Arthritis of the Hip. (Osteocondromatosi e artrosi coxofemorale.) GARELLI, R. (1959). *Reumatismo*, **11**, 277. 16 refs.

Haemophilic Osteo-Arthropathy. (Les ostéo-arthropathies hémophiliques.) LAYANI, F., MAY, V., PAQUET, J., and PELISSON, J. (1959). *Sem. Hôp. Paris*, **35**, 3435. 14 figs, 51 refs.

Anginal and Pseudo-anginal Syndromes in Patients with Vertebral Osteo-arthritis. (Sulle sindromi anginose e pseudo-anginose in pazienti con artrosi vertebrale.) CHIARIONI, T., CANTARELLI, G., and NARDI, E. (1959). *Policlinico, Sez. med.*, **66**, 433. 19 refs.

(Spondylitis)

Incidence of Genital Infection in Male Patients with Ankylosing Spondylitis. OATES, J. K. (1959). *Brit. J. vener. Dis.*, **35**, 89. 18 refs.

The incidence of genital infection in 82 male patients suffering from ankylosing spondylitis was investigated at the London Hospital. Previous similar studies of this subject are reviewed and the criteria for diagnosis of ankylosing spondylitis and chronic prostatitis are defined. Patients with ankylosing spondylitis as a complication of Reiter's disease and those in whom it had been recognized at the venereal disease clinic were excluded from the study.

All patients were questioned as to past genital infection, and the prostatic secretion was examined in the 72 cases in which it could be obtained; of these, sixty (84 per cent.) showed evidence of chronic prostato-vesiculitis. The author compares this with a maximum incidence of 25 to 30 per cent. in a control series of normal healthy males previously examined by him. Of the whole group of

patients, nine were found to have mild non-specific urethritis, while a further nine gave a history of gonorrhoea, three a history of non-specific urethritis, and eight a history of urethral infection of undetermined origin. The results of this study appear to add weight to the suggestion that there is a close link between ankylosing spondylitis and genital infection, whether gonococcal or non-gonococcal, and the author speculates on the possible prophylactic effect of the efficient treatment of genital infections. *Leslie Watt.*

Significance of Sacro-iliitis in Reiter's Disease. CSONKA, G. W. (1959). *Brit. J. vener. Dis.*, **35**, 77. 3 figs, 8 refs.

Writing from St. Mary's Hospital, London, the author describes the results of re-examination of 134 out of 166 patients with Reiter's disease previously reported (*Brit. med. J.*, 1958, **1**, 1088; *J. Fac. Radiol.* (*Lond.*), 1958, **9**, 44; *Abstr. Wld Med.*, 1958, **24**, 179 and 238). All were examined or re-examined radiologically for evidence of sacro-iliitis and 27 (20·1 per cent.) were found to have such evidence. The progress and clinical features in the two groups of patients, that is, those with and those without sacro-iliitis, are compared with each other and also with the course in fifty consecutive cases of classic ankylosing spondylitis seen at the hospital over the same period.

It is concluded that the development of sacro-iliitis in Reiter's disease generally indicates that the illness was more severe from the start even though sacro-iliac joint lesions were not an important or persistent cause of symptoms. Reiter's disease with sacro-iliitis differs significantly from ankylosing spondylitis notably in regard to age and sex incidence, type of onset, proportion of peripheral joint and spinal involvement and incidence of iritis. Conjunctivitis, keratodermia, balanitis, and plantar fasciitis, which are prominent in Reiter's disease, do not occur in ankylosing spondylitis. The relatively high incidence of rheumatoid arthritis in the families of patients suffering from Reiter's disease suggests that further investigation is warranted. The author concludes that, at least for the present, Reiter's disease and ankylosing spondylitis should be regarded as separate entities. *Leslie Watt.*

Ankylosing Spondylitis: Results of Treatment and, Their Presentation. O'CONNELL, D. (1959). *J. Fac. Radiol.* (*Lond.*), **10**, 156. 1 ref.

The results obtained with radiotherapy in 87 cases of ankylosing spondylitis seen at Charing Cross Hospital, London, are described. A single course of treatment was given, with a dosage of 600 to 300 r. to the bone marrow and an integral dose of 5 to 7·5 mg./r. This was supplemented by physiotherapy and when necessary for associated depression by psychotherapy.

The cases were classified according to the severity of the disease before and the degree of remission after treatment. Of the 87 patients 75 were in remission or had made a complete recovery after 3 months' treatment; of 74 followed up after 5 years 36 were in remission. Patients with a mild form of the disease appeared to respond more completely and more consistently to radiotherapy. *M. Wilkinson.*

Procto-colitis and Other Pelvic Infections in Relation to Ankylosing Spondylitis, with a Note on the Vertebral Venous System. GRAINGER, R. G. (1959). *J. Fac. Radiol.* (*Lond.*), **10**, 138. 17 figs, bibl.

In this paper from St. Thomas's Hospital, London, the author discusses the evidence for the view that pelvic infection may precipitate ankylosing spondylitis in susceptible subjects, and describes seven new cases of ulcerative colitis with sacro-iliitis or classic ankylosing spondylitis. In six of the cases in which the history was adequate the arthritis began within 3 years of the onset of colitis. He points out that a review of the literature suggests that the association of these diseases is too frequent to be due to chance. He also briefly refers to two cases of Crohn's disease with bilateral sacro-iliitis. The progression of Reiter's syndrome to ankylosing spondylitis is illustrated in three case histories. The sacro-iliac arthritis of Reiter's syndrome may be more frequently unilateral but is otherwise difficult to distinguish from ankylosing spondylitis. The sacro-iliac and spinal changes in paraplegia are described and their possible relationship to chronic urinary infection is discussed. Involvement of the sacro-iliac joints in rheumatoid arthritis is considered to be uncommon and never a dominant feature of the clinical picture.

There is evidence in the literature which suggests that prostato-vesiculitis is frequent in patients with ankylosing spondylitis, and the thesis that pelvic infection may cause non-suppurative bone lesions is supported by the findings in two cases—one with bilateral sacro-iliac changes after a septic abortion and one with osteitis pubis and ischii following post-prostatectomy sepsis.

Discussing the vertebral venous system the author suggests that through this channel pelvic infection may cause sacro-iliac changes which in genetically predisposed patients may herald the development of classic ankylosing spondylitis. [He does not attempt to explain the occurrence of peripheral arthritis in this condition.] *M. Wilkinson.*

Changes in the Duration of Vibration Sense in Ankylosing Spondylitis. (Änderung der Dauer der Vibrationsempfindung bei Bechterewscher Krankheit.) IRÁNYI, J., and RIESZ, E. (1959). *Z. Rheumaforsch.*, **18**, 211. 14 refs.

At the State Institute of Rheumatology, Budapest, the duration of the vibration sense was investigated by means of a tuning fork in 250 patients with various rheumatic disorders. It was found that the vibration sense was prolonged to about twice the normal duration in the majority of 100 patients with ankylosing spondylitis. The reason for this finding is not known, but it is suggested that it may be due to irritation of the posterior nerve roots as a result of the narrowing of the intervertebral foramina in this disorder. *G. W. Csonka.*

Ankylosing Spondylitis and Rheumatic Iritis. LENOCH, F., KRALIK, V., and BARTOS, J. (1959). *Rev. Czech. Med.*, **5**, 89. 7 refs.

Spondylarthritis Ankylopoietica associated with Iritis. LAITINEN, H., PELTOLA, P., and SARAJAS-KYLLÖNEN, S. (1959). *Ann. Med. intern. Fenn.*, **48**, 87. 7 figs, 20 refs.

Ankylosing Spondylitis. MASON, R. M. (1959). *Brit. J. vener. Dis.*, **35**, 71. 1 fig., bibl.

Reiter's Disease and Ankylosing Spondylitis. Is there a Common Cause? OATES, J. K. (1959). *Brit. J. vener. Dis.*, **35**, 81. 29 refs.

(Miscellaneous)

Periarthritis of the Shoulder: a Study of the Disease and Its Treatment. LLOYD-ROBERTS, G. C., and FRENCH, P. R. (1959). *Brit. med. J.*, **1**, 1569. 4 refs.

This paper from St. George's Hospital, London, represents a careful study of the results of treatment in 59 cases of periarthritis of the shoulder of a standard minimum level of severity and duration.

It has long been recognized that manipulation under anaesthesia in the acute, irritable phase generally fails to restore movement permanently and often causes an exacerbation of symptoms with a further loss of movement, whereas manipulation at a later and more quiescent phase will generally free movement without risk of recrudescence. The authors wished to discover whether, with the addition of a potent anti-inflammatory agent such as hydrocortisone injected into the joint cavity, manipulation could be carried out successfully in the acute phase and the duration of the disability shortened; nineteen cases were treated this way, 25 mg. hydrocortisone being injected at the same time as manipulation was carried out under anaesthesia and active physiotherapy given subsequently, while thirteen cases were treated with 2·5 g. cortisone given orally over a period of one month, together with supervised active movements and palliative physiotherapy. The remaining 27 cases were treated by physical methods, sometimes followed by late manipulation under anaesthesia, but received no steroids.

The use of intra-articular cortisone combined with manipulation under anaesthesia followed by active physiotherapy was found to give considerably more satisfactory results than did the alternative methods of treatment, and the total period of disability was shortened.

W. S. C. Copeman.

Effectiveness of Multiple Short-interval Intra-articular Injections of Hydrocortisone Acetate in Rheumatoid and Osteo-Arthritis. BONNER, C. D. (1959). *Arch. inter-amer. Rheum.*, **2**, 3. Bibl.

At the Holy Ghost Hospital, Cambridge, Massachusetts, sixteen patients with rheumatoid arthritis and 31 with osteo-arthritis were given courses of intra-articular injection of hydrocortisone in which the interval between the injections did not exceed 2 or 3 days. The usual course consisted of three to six injections. The rheumatoid patients received a total of 116 injections in 37 courses and the osteo-arthritic patients 214 injections in 61 courses. [It should be noted that eight of the patients with rheumatoid arthritis were also receiving systemic steroid therapy.]

An "excellent" or "good" response was obtained to 32 of the 37 courses given to patients with rheumatoid arthritis, the remission in some three-quarters of these instances lasting more than 2 months. Of the 61 courses given to patients with osteo-arthritis "excellent" or "good" results were obtained in response to 58.

From a review of the literature the author found that these results were much better than those hitherto reported.

K. C. Robinson.

Untoward Effects of Phenylbutazone (Butazolidin)—a Re-evaluation. SPERLING, I. L. (1959). *Arthr. and Rheum.*, **2**, 203. 26 refs.

The results of phenylbutazone therapy in 590 adult patients (aged 19 to 75 years) suffering from various rheumatic disorders are reported. The daily dose ranged from 100 to 800 mg., the average daily maintenance dose being 200 mg. In 54 cases treatment was given for at least one year. Excellent or good results were obtained in 34 out of 78 cases of rheumatoid arthritis, in 95 out of 115 cases of osteo-arthritis, and in all ten cases of ankylosing spondylitis. It was necessary to discontinue treatment in thirty of the 55 cases in which undesirable reactions occurred. These reactions, which were observed more frequently in patients with rheumatoid arthritis than in those suffering from other forms of rheumatism, included rashes and gastro-intestinal distress. Leucopenia developed in two patients. For the most part, the reactions occurred within the first month of treatment and when the daily dose exceeded 300 mg.

In view of these results the author recommends that phenylbutazone should be administered with caution in cases of heart disease. Fluid retention must be avoided, especially in the elderly, and for this purpose the dosage of the drug must be low and any gain in weight must be checked. The drug must not be given on an empty stomach. Antacids may be of use if mild gastro-intestinal symptoms develop. The amount of salt in the diet should be restricted in all cases. Phenylbutazone therapy is contraindicated in patients with a history of peptic ulcer. During the early stages of treatment a complete blood count is performed weekly; later, the blood is examined at intervals of 4 to 6 weeks. The patient is warned to report immediately the occurrence of untoward signs and symptoms such as pruritus, rash, sore throat, fever, gastro-intestinal disturbances, and tarry stools. The author considers that when these precautions are observed long-term therapy with phenylbutazone is likely to prove both safe and effective in the management of rheumatoid arthritis, ankylosing spondylitis, and other chronic forms of rheumatism.

A. Garland.

Sterno-clavicular Arthrosis. (L'arthrose sterno-claviculaire.) DE SÈZE, S., DJIAN, A., and KHALAF, S. (1959). *Rev. Rhum.*, **26**, 123. 9 figs.

This paper is based on a clinical and radiological study of sterno-clavicular arthrosis, of which some ten cases are

seen annually at the Hôpital Lariboisière, Paris. Both sexes may be affected, but most often the patient is a post-menopausal woman engaged on manual work. The right side is more commonly attacked than the left and the condition is often preceded by scapulo-humeral periarthritis on the same side. Examination reveals a swelling over the sterno-clavicular joint; radiologically this is shown to be due to antero-medial subluxation of the sternal end of the clavicle, and when the shoulders are braced back the swelling disappears. There is usually no pain and there are no signs of inflammation. Radiographs show the presence of osteophytes. The condition is benign and the prognosis is good, the main interest of this trivial ailment being its correct diagnosis, since the pseudo-tumoral appearance of the lesion may occasionally give concern to both doctor and patient.

G. Loewi.

Prednisolone Trimethylacetate in Intra-articular Therapy. MURDOCH, W. R., and WILL, G. (1959). *Brit. med. J.*, **1**, 1267. 1 fig., 21 refs.

An investigation of the value of intra-articular injection of prednisolone trimethylacetate in the treatment of arthritis was undertaken at Glasgow Royal Infirmary, the injections being given into the knee-joints of 27 patients with active rheumatoid arthritis, six with osteo-arthritis, and two with recurrent hydrarthrosis. The knee-joint was entered from the lateral aspect at the level of the upper border of the patella. A small amount of fluid was removed for analysis, but no attempt was made to drain the joint. The standard dose of prednisolone trimethylacetate for injection into the knee was 20 mg., and initially the interval between injections was 7 days, until the effusion had resolved; thereafter the injections were gradually spaced out and eventually stopped. The average follow-up period after the last injection was 6·1 months. In rheumatoid arthritis the results at the end of the follow-up period were good in 23 cases, fair in two (regular maintenance injections being necessary), and poor in two. The results were good in two cases of osteo-arthritis, fair in two, and poor in two. Good results were obtained in both cases of hydrarthrosis.

In ten patients with bilateral effusions the effect of prednisolone trimethylacetate was compared with that of lignocaine, one knee being injected with prednisolone trimethylacetate and the other with an equal volume of lignocaine. Prednisolone trimethylacetate was more effective than lignocaine in reducing the amount of pain and swelling.

The authors conclude that prednisolone trimethylacetate is an effective agent for intra-articular therapy.

C. E. Quin.

Synovial Fluid Changes in Intra-Articular Therapy: Effect of Prednisolone Trimethylacetate. MURDOCH, W. R., and WILL, G. (1959). *Brit. med. J.*, **1**, 1271. 2 figs, 16 refs.

At Glasgow Royal Infirmary the authors studied the cytological and biochemical changes in the synovial fluid from the knee-joints of patients with arthritis. Altogether 57 knee-joints were aspirated, suitable serial specimens being obtained from forty (rheumatoid arthritis in thirty, osteo-arthritis in six, and hydrarthrosis in four). Injections of prednisolone trimethylacetate were given at weekly intervals, and before each injection a small amount of fluid was withdrawn for study of the total and differential cell counts, total protein content, mucin content, viscosity, and electrophoretic pattern. During treatment with prednisolone trimethylacetate there was a fall in the cell count, due mostly to a sharp diminution in polymorphonuclear leucocytes, although there was also a real fall in lymphocytes and monocytes. Initially the average protein content was 4·4 g. per 100 ml.; after prednisolone treatment it fell to 3·4 g. per 100 ml. Electrophoresis showed a rise in the albumin content of the fluid in most cases. The changes in the cell count occurred after the first two injections, but the changes in the protein content occurred more gradually. The viscosity of the synovial fluid from 26 rheumatoid joints rose and the mucin content of fluid from 27 similar joints fell. The initial cell count and total protein were lower in the synovial fluid from osteo-arthritic joints, but the change after intra-articular therapy followed the same pattern as those observed in the fluid from joints affected by rheumatoid arthritis. In ten patients with bilateral effusions one knee was injected with lignocaine. No change in viscosity or mucin content of the fluid was observed; the cell count rose in six and was unchanged in four, while the protein content rose in four and was unchanged in six. An analysis of the electrophoretic pattern in this group showed no significant changes.

C. E. Quin.

Bacteriological and Biochemical Investigations in Reiter's Syndrome. CSONKA, G. W. (1959). *Brit. J. vener. Dis.*, **35**, 84. 19 refs.

In this paper the author has assembled the results of laboratory tests performed on the series of cases of Reiter's syndrome previously reported. The tests were all carried out in London, at St. Mary's Hospital, the Wright-Fleming Institute, the Lister Institute, and the London Hospital. For various reasons not all the tests were performed in every case and there was therefore a slight over-representation of severe cases of the disease.

Controlled bacteriological and serological tests for pleuro-pneumonia-like organisms showed that they were not a significant factor in Reiter's syndrome. Nor is the gonococcus considered likely to be of primary aetiological significance for various reasons, in spite of the fact that this organism was isolated from 107 of 195 cases examined. The gonococcal complement-fixation test was of little practical value, but may occasionally draw attention to the presence of unsuspected venereal infection. Culture of the urine of patients without gonorrhoea revealed nothing of significance in the absence of complicating organic lesions, but examination of the prostatic secretion revealed that 55 per cent. of 132 patients had prostatitis according to the generally accepted criteria; the full significance of this finding, however, cannot be assessed because of the lack of a control group. Moderate normocytic anaemia was present in 15·9 per cent. of 88 patients, and some degree

of neutrophil leucocytosis was present in one-third of the patients tested. A raised erythrocyte sedimentation rate was usually associated with active disease, especially when active arthritis was present. Electrophoretic analysis of the serum protein pattern in thirty patients showed a decrease in the albumin fraction and an increase in the α-globulin fractions; it is suggested that these changes, though not specific for Reiter's syndrome, warrant further study. The differential agglutination test, the L.E.-cell test, the identification in the serum of C-reactive protein, and estimation of the serum uric acid level are of value only in the differential diagnosis.

Leslie Watt.

Reiter's Disease. BAILEY, H., and BISHOP, W. J. (1959). *Brit. J. vener. Dis.*, **35**, 101. 1 fig., bibl.

This, with the preceding abstract and other articles in the same issue of the *Brit. J. vener. Dis.*, comprises a comprehensive discussion on our present knowledge of Reiter's disease—a disease characterized by non-gonococcal purulent urethritis, followed by arthritis, conjunctivitis, and anterior uveitis. The suggestion is made, particularly in male patients, that the primary lesion is a genito-urinary infection, usually a prostatovesiculitis which gives rise to various forms, the most common of which is spondylitis. The infective agent is unknown but it is suggested that the clinical variations may be due to such factors as genetic predisposition and the effect of repeated infections. [The final article has appended a select bibliography covering the years from 1916 to 1959.] *Stewart Duke-Elder.*

Diagnostic Difficulties in a Case of Juvenile Chronic Ankylosing Polyarthritis with Blindness and Chondroarthrodysplasia associated with Scleroderma. (Difficoltà dignostiche in un caso di poliartrite cronica anchilosante giovanile con ceità e condro-atrodisplasia associata a sclerodermia.) DELLA CASA, R. (1958). *Minerva pediat.* (*Torino*), **10**, 1234. 30 figs, 19 refs.

Ocular Manifestations in Rheumatic Diseases in Children. (Sulle manifestazioni oculari della malattia reumatoide dell'infanzia.) D'ARRIGO, P. (1958). *Arch. Ottal.*, **62**, 391. 4 figs, 53 refs.

Excretion of Uropepsin after the Intravenous Administration of Sodium Salicylate. (L'eliminazione di uropepsina dopo somministrazione endovenosa di salicilato di sodio.) ZANGARA, A., SICCARDI, A., and GAZZANO, A. (1959). *Reumatismo*, **11**, 258. 5 figs, 48 refs.

Reiter's Syndrome. KESTEL, J. L., HARRIGAN, J. J., and SMITH, A. L., JR. (1959). *Neb. St. med. J.*, **44**, 111. 5 refs.

Reiter's Syndrome. (Sindome di Reiter.) LUCHERINI, T., and CECCHI, E. (1958). *Reumatismo*, **10**, 151. 10 figs, 17 refs.

Mucocutaneous Lesions of Reiter's Syndrome. MONTGOMERY, M. M., POSKE, R. M., BARTON, E. M., FOXWORTHY, D. T., and BAKER, L. A. (1959). *Ann. intern. Med.*, **51**, 99. 6 figs, 6 refs.

Some Considerations in the Employment of Arthritics in Industry. FRENKIL, J. (1959). *A.M.A. Arch. industr. Hlth*, **20**, 359. 19 refs.

Primer on the Rheumatic Diseases. Part 1. Prepared by a Committee of the American Rheumatism Association (1959). *J. Amer. med. Ass.*, **171**, 1205.

Association of Multiple Arthritis with Carcinoma. PATHY, M. S. (1959). *Rheumatism*, **15**, 73. 14 refs.

Ochronosis and Alcaptonuria. (Ochronose et Arthrite Alcaptonurique.) DUPUIS, P.-V., WATILLON, M., DESPONTIN, J., and DETHIER, J. (1959). *Rev. Rhum.*, **26**, 473. 12 figs, 44 refs.

Spinal Joint Changes and Dental Infections. INGELMARK, B. E., MØLLER-CHRISTENSEN, V., and BRINCH, O. (1959). *Acta anat.* (*Basel*), **38**, Suppl. 36.

Studies on the Renal Excretion of Salicylate in the Dog. WEINER, I. M., WASHINGTON, J. A., and MUDGE, G. H. (1959). *Bull. Johns Hopk. Hosp.*, **105**, 284. 3 figs, 31 refs.

Micoplasmal (PPLO) Polyarthritis and Tumour Regression in Rats. HOWELL, E. V., WARD, J. R., and JONES, R. S. (1959). *Proc. Soc. exp. Biol.* (*N.Y.*), **102**, 210. 1 fig., 12 refs.

Amyloidosis in Chronic Polyarthritis. (Über amyloidose bei chronischer polyarthritis.) FRENGER, W., GÖTZ, H., and SCHEIFFARTH, F. (1959). *Z. Hyg. Infekt.-Kr.*, **146**, 166. 3 figs, 53 refs.

Lumbago Treated with Local Injections of Hydrocortisone. (Lumbago behandlet med hydrocortison lokalt.) KROGNESS, K. G. (1959). *T. norske Laegeforen.*, **79**, 1349. 2 figs, 6 refs.

Guillain-Barré Syndrome and Acute Articular Rheumatism. (Sindrome di Guillain-Barré e reumatismo articolare acuto.) BERTONI, L., and BELLOTTI, G. (1959). *Reumatismo*, **11**, 286. 32 refs.

Local Changes in Experimental Arthritis and the Effect on them of Hyaluronidase. LÖFGREN L. (1959). *Ann. Med. exp. Fenn.*, **37**, 276. 4 figs, 28 refs.

Observations on the Histology of Ageing Human Connective Tissues. BICK, E. M. (1959). *J. Mt Sinai Hosp.*, **26**, 501. 2 figs, 12 refs.

Differentiation of Atypical Cases of Chronic Polyarthritis. (Zur Differenzierung atypischer Fälle von chronischer Polyarthritis.) KOVÄCS, L. (1959). *Z. Rheumaforsch.*, **18**, 292. 18 refs.

Technique and Results of Local Hydrocortisone and Prednisolone Therapy. (Methodik und Ergebnisse lokaler Hydrocortison- und Prednisolon-Therapie.) ROSENFELD, W. (1959). *Med. Klin.*, **54**, 1642. 11 refs.

Rheumatic Aetiology of Hepatic Cirrhosis. (Zur Frage der rheumatischen Ätiologie der Lebercirrhose.) KNORRE, D. (1959). *Frankfurt. Z. Path.*, **70**, 68. 31 refs.

Histochemical Studies of Gold in Gold Dermatitis before and after B.A.L. Treatment. (Histochemische untersuchungen über das Gold bei der Golddermatitis vor und nach Bal-Behandlung.) EDSTRÖM, G., and VOIGT, G. E. (1959). *Acta rheum. scand.*, **5**, 165. 1 fig., 4 refs.

Effect of Hyaluronidase and Toluidine Blue on the Mast Cells in Rats and Hamsters. GUSTAFSSON, B. E., and CRONBERG, S. (1959). *Acta rheum. scand.*, **5**, 179. 1 fig., 21 refs.

Pressure Measurements in Human Striated Muscles during Contraction. SYLVEST, O., and HVID, N. (1959). *Acta rheum. scand.*, **5**, 216. 4 figs, 11 refs.

Veins and Rheumatism. (Veines et rhumatismes.) FRANÇON, F. (1959). *Méd. phys. Rhum.*, **14**, 151.

Development of an Acute Polyarthritis in Rats treated with Prolactin. JASMIN, G. and BOIS, P. (1959). *Arthr. and Rheum.*, **2**, 460. 1 fig., 10 refs.

Disk Syndrome

Cervical Spondylosis: Pilot Therapeutic Trial. STEINBERG, V. L., and MASON, R. M. (1959). *Ann. phys. Med.*, **5**, 37. 4 figs, 8 refs.

The authors describe a pilot study of three commonly used physical methods of treatment of cervical spondylosis which they carried out at the London Hospital on 163 patients complaining of neck and/or shoulder pain, or peripheral paraesthesiae attributable to this condition. The treatment regimens were:

(1) heat, massage, and longitudinal neck traction given for one-hour periods three times a week for one month (42 patients);
(2) the fitting of a felt collar reinforced with plastic, this to be worn as much as possible and especially during sleep (22);
(3) neck and shoulder girdle exercise (six patients in each class), these being given for half an hour three times a week for one month (29).

A fourth smaller control group (seven patients, Group 0) was treated according to the physician's free choice of method.

Allocation to the various treatment groups was made by reference to the last digit of the patient's hospital registration number; by chance this method unfortunately resulted in a very uneven distribution, and the authors comment on the advisability of a truly random allocation. The age incidence was highest in the 10-year age group 40 to 49, and was reasonably consistent between the groups. All patients were reviewed after 2 and 4 weeks' treatment, and assessment of the result, being dependent mainly on relief of pain, was entirely subjective.

The results in 146 patients (seventeen having defaulted) showed that, after 4 weeks, the felt collar gave the best "improvement" rate (81·8 per cent.), this rate in Groups 0, 1, and 3 being 69·2, 70·5, and 71·8 per cent. respectively. Group 3 (the exercise group) showed the highest "cure" rate (15·4 per cent.), but also the highest defaulter rate (13·3 per cent.), and the highest aggravation rate (12·8 per cent.). Patients in Group 0 (the "physician's free choice" group) did not do particularly well, and the authors therefore consider that the method of arbitrary selection of treatment employed was quite justified. They also point out that the apparently most effective treatment, that is, the fitting of a collar, is the one most sparing of time for both patient and physiotherapist. They stress, however, that this was a pilot trial only, and much larger numbers of patients, including a placebo group, would have to be studied to provide definite results. *B. E. W. Mace.*

Inflammatory Intervertebral Disk Disease as a Complication of the Operative Treatment of Lumbar Herniations. STERN, W. E., and CRANDALL, P. H. (1959). *J. Neurosurg.*, **16**, 261. 3 figs, 17 refs.

From the University of California Medical Center, Los Angeles, the authors report nine cases in which inflammatory lesions appeared in the intervertebral space following surgery for herniation of a lumbar disk. Case histories are given and radiographs reproduced. In three cases there was acute and obvious suppuration in the operation wound, another patient developed meningitis, and in a fifth case there was some discharge from the wound, but no organisms could be cultured. The remaining four patients showed no evidence of frank suppuration, but had disabling lumbar pain. Such pain was the characteristic feature of the clinical picture; it often spread to the groin and lower abdomen and was sometimes associated with paravertebral muscle spasm. In the acute suppurative cases clinical evidence of infection was amply apparent. Radiological changes, which were first noted 2 months after operation and in some cases for up to 2 years, consisted in extensive destruction of adjacent vertebral bodies with, later, bony fusion between them.

In regard to treatment, the frankly suppurating lesions were treated along usual lines, including open drainage, later secondary closure, and appropriate antibiotic therapy. The non-suppurating cases were treated con-

servatively; in these cases immobilization of the spine and antibiotic treatment did not appear to affect the progress of the disease. Although bacterial agents were probably responsible for the majority of these cases, other processes may have been involved. In some, for example, it is possible that the naturally occurring progression of degenerative disease of the joint, aggravated by surgical trauma, might have accounted for the clinical and radiological changes observed. *Brodie Hughes.*

Re-operation for Sciatica. (Les réinterventions pour sciatique.) SICARD, A., and GÉRARD, Y. (1959). *J. Chir.* (*Paris*), **78**, 113.

The authors describe the circumstances in which a surgeon may be compelled to perform further operations on the spine of a patient who has already had one or more operations for prolapsed intervertebral disk. These second (or even third) operations are always difficult and require considerable skill not only in performance but in the selection of cases. Among the reasons for re-operation are failure of the original operation to benefit the patient; true relapse (defined as recurrence of sciatica at the same level after a period of freedom following the first operation); or subsequent development of sciatica at another segmental level or on the opposite side. Myelography should be performed in all cases before deciding to operate. Definite radiological evidence of a localized protrusion strongly indicates operation, but a negative myelogram counsels caution.

In reviewing their own experience at the Hôpital Beaujon, Paris, of 87 re-operations (59 patients formerly operated by one of the authors and 28 initially operated on elsewhere) the authors conclude that these further explorations are negative in the majority of cases, apart from those in which a herniated intervertebral disk had been missed or incompletely removed on the previous occasion. Those patients do best in whom a new herniation is found and removed, but section of nerve roots sometimes brings benefit in cases in which the second exploration gives negative results. Early re-intervention produces better results (100 per cent. of sixteen cases cured) than do later re-operations (56 per cent. cured, 26 per cent. improved, and eighteen failures in 66 cases). A third operation was rarely of benefit. *J. B. Stanton.*

Hyperostotic Discosomatic Vertebral Arthrosis. (Artrosi disco-somatica iperostosante vertebrale.) ROBECCHI, A. (1959). *Minerva med.* (*Torino*), **50**, 2125. 13 figs, 8 refs.

The condition first described by Forestier and Rotes-Querol (*Ann. rheum. Dis.*, 1950, **9**, 321; *Abstr. Wld Med.*, 1951, **9**, 641) as senile ankylosing hyperostosis of the spine, but which the present author prefers to call hyperostotic discosomatic vertebral arthrosis, has received little attention in the literature of rheumatism. In the opinion of the author many cases escape diagnosis even after radiological examination, so that errors occur both in prognosis and in treatment, while some cases have even found their way into the literature labelled ankylosing spondylitis.

Figures are quoted to show that the condition is commoner than is generally supposed. It occurs especially in older patients, and occupational and family history have little bearing on the diagnosis, which is often made by chance on the basis of a radiograph taken for some other purpose. The level and extent of spinal involvement vary widely. The characteristic bony lesion occurs most commonly in the thoracic region, particularly on the right side. Peripheral joints and bony surfaces far from joints may also be affected. Because the disease so often attacks the aged, kyphosis is not necessarily significant. Local or generalized pain or stiffness are the commonest symptoms. Although the bony lesion is usually thoracic, yet it is in the lumbar region that the patient usually feels the pain, which is often aggravated by movement or prolonged standing, is most obvious first thing in the morning, and tends to pass off as the day wears on. Rest in the horizontal position reduces and may abolish it. Unlike that of inflammatory spinal disease the pain of this condition does not occur at night, and it is never referred remotely. Physical examination may be no more informative than the history. Forced movement of the spine sometimes increases the pain, but tenderness on pressure over the spinous processes or near the transverse processes is rare. There is often some stiffness in peripheral joints such as the hip and shoulder. In a series of more than twenty cases [exact number not stated] seen at the Turin Rheumatological Centre the author was unable to confirm the occurrence of psychiatric disturbance, such as depression, described by other authors. Haematological changes, such as raised erythrocyte sedimentation rate (E.S.R.), and circulatory disorders, such as hypertension, were notably absent. Diagnosis may be possible only by radiography. The characteristic appearance is of new bone formation which appears to have "dripped" down the right half of the thoracic spine. Protrusion of the intervertebral disks may enforce a convex, bridge-like appearance on the new bone as it crosses the intervertebral spaces. Arthritis may affect the various intervertebral joints and there may be osteophyte formation. The normality of the sacro-iliac joints is important in the differential diagnosis from ankylosing spondylitis, which also occurs at an earlier age and may be associated with systemic symptoms and a raised E.S.R.

The symptoms are frequently mild or absent and the outlook good. The organic changes show no regression, yet the symptoms are intermittent and intervals of freedom may last for months or even years. Rest is important in the relief of pain, as also are antirheumatic and analgesic drugs. The author gives first place in treatment to phenylbutazone, provided there are no contraindications. Aspirin may also help, but steroids are useless. Any physiotherapy must be determined by the needs of the individual case.

The author sets out the various views as to the origin and nature of the disease: that it is a link between ankylosing spondylitis and rheumatoid arthritis; that it is due to metaplastic ossification of the anterior longitudinal ligament; that it is a normal component of the ageing process; and that it is a separate disease. He himself belongs to a school that sees it as a form of spinal

arthritis. He finds it difficult to account for the anatomical localization and examines various theories.

A. C. F. Green.

Topographic Changes in the So-called Latero-vertebral Sympathetic Chain in Arthrosis and Disk Lesions of the Lumbo-sacral Spine. (Altérations topographiques de la chaine sympathique dite latéro-vertébrale dans les arthroses et discopathies de la colonne lombo-sacrée.) DECHAUME, J., DUROUX, P., and ANTONIETTI, C. (1959). *J. Med. Lyon*, **952**, 769. 5 figs.

Effect of Conservative Treatment of Lumbago-Sciatica. (Effekten af konservativ behandling ved lumbago-ischias.) FRANTZEN, E., and ZACHARIAE, L. (1959). *Nord. Med.*, **62**, 1509. 13 refs.

Treatment of Lumbo-sciatic Pain with Water-soluble Prednisolone by the Sacral Epidural Route. (Il prednisolone idrosolubile per via epedurale sacrale nelle lombosciatalgie.) FRAGASSO, V. (1959). *Gazz. med. ital.*, **118**, 358. 12 refs.

Disk Herniation and Lumbo-sciatic Pain. (Discoartropatías y lumbosacralgia.) OLIVES, J. B. (1959). *Rev. esp. Reum.*, **8**, 44. 32 refs.

Cervical Whiplash Injury. HACKETT, G. S. (1959). *Rheumatism*, **15**, 64. 3 figs, 7 refs.

Gout

Gout. A Clinical and Therapeutic Study. (La goutte. Étude clinique et thérapeutique.) DE SÈZE, S., RYCKEWAERT, LEVERNIEUX, J., and MARTEAU, R. (1959). *Rev. Rhum.*, **26**, 81. Bibl.

The authors report, from the Hôpital Lariboisière, Paris, a study of the clinical manifestations, antecedent history, and site affected in one hundred cases of gout in which the disorder was characterized by typical painful crises responding to colchicine. At the time of study the disease had been present in all cases for at least 10 years. Of the hundred patients, of whom only four were female, 37 gave a family history compatible with gout, while seventy described a prodromal symptom, in nine cases associated with calculus in the renal tract. The first attack usually involved the metatarso-phalangeal joint of the big toe, and this joint was involved throughout the course of the disease in 96 per cent. of the cases. The joints next involved, in descending order of frequency, were the knee, ankle, other foot joints, elbow, and wrist. Polyarthritis occurred in six cases, while 59 patients had tophi and 22 had renal colic at some time in the course of their history. Of 75 patients investigated, eight had proteinuria, ten azotaemia, and nine a urea clearance of less than 50 per cent. Renal manifestations were commoner in cases of gout with tophi than in those without tophi. In 96 of the hundred cases the blood uric acid level exceeded 6 mg. per 100 ml. at some stage [method of determination not stated]. Out of eighty cases examined radiologically, osteo-cartilaginous lesions were observed in the feet in 66 and in the hands in 41. In discussing treatment the authors state that they favour the use of colchicine or phenylbutazone as therapeutic agents.

G. Loewi.

Gouty Syndrome of Tietze. Acute Cartilaginous Gout. (Le syndrome de Tietze goutteux. Goutte aiguë des cartilages.) MUGLER, A. (1959). *Rev. Rhum.*, 26, 113. 10 refs.

The author describes 32 cases in which pain was localized over a costo-chondral junction, the commonest site affected being the 3rd left junction. There were no superficial signs of inflammation, but in all except one case there was pain on local pressure. The author regards this as a manifestation of gout, since in eighteen cases the maximum blood uric acid levels ranged from 5·5 to 11·1 mg. per 100 ml. [a finding impossible to evaluate, since the method of determination and the normal range are not given]; it is further stated that some other manifestation of gout was present at some stage [but no details are offered]. Improvement followed treatment with colchicine, or local injection of procaine or hydrocortisone. The importance of differentiating this gouty condition involving a costo-vertebral articulation from the anginal pain associated with coronary arterial disease is stressed.

G. Loewi.

Effect of Chlorothiazide Therapy on Serum Uric Acid and Uric Acid Excretion. MONROE, K. E., GRANT, L. H., SASAHARA, A. A., and LITTMANN, D. (1959). *New Engl. J. Med.*, **261**, 290. 1 fig., 7 refs.

In nine patients undergoing long-term chlorothiazide therapy for various cardiovascular diseases at the Veterans Administration Hospital, West Roxburg, Massachusetts, the serum uric acid level and uric acid excretion were determined during treatment and 7 to 10 days after chlorothiazide was discontinued. The serum uric acid level was high in seven of the nine patients during treatment (average 7·8 mg. per 100 ml.; range 3·9 to 10·4 mg. per 100 ml.) and fell in every case at the second estimation 7 to 10 days after discontinuing the drug (average 6·0 mg. per 100 ml.; range 3·7 to 7·8 mg. per 100 ml.). Chlorothiazide administration was resumed, and 6 weeks later the serum uric acid level was again rising. The urinary excretion of uric acid behaved in the opposite manner. Since there was no rise in blood urea nitrogen level the glomerular filtration was not significantly reduced, and it is suggested that chlorothiazide (in these relatively low doses) blocked the tubular excretion of uric acid.

None of the patients had a gouty diathesis or symptoms attributable to the hyperuricaemia.

T. B. Begg.

Gout: Six-year Follow-up on Probenecid (Benemid) Therapy. BARTELS, E. C., and MATOSSIAN, G. S. (1959). *Arthr. and Rheum.*, **2**, 193. 4 figs, 10 refs.

Between 1951 and 1958 at the Lahey Clinic, Boston, probenecid was given in the treatment of 231 patients suffering from gout. The dosage of the drug was 0·5 to 1 g. daily, and with each 0·5 g. probenecid 0·5 mg.

colchicine were also administered. The dosages were adjusted so that the serum uric acid level did not exceed 6 mg. per 100 ml. In one patient given 0·25 g. of probenecid daily for more than 3 years the serum uric acid level was maintained at approximately 4 mg. per 100 ml. Two months after treatment was discontinued the level rose sharply to 7·5 mg. per 100 ml. Comparatively high serum levels of uric acid were detected in patients with renal disease.

Patients were advised to abstain from alcohol and to restrict the amount of purines and fat in the diet. In order to avoid precipitating an acute attack of gout no attempt was made to bring about a reduction in weight until the disease was under good control. In the first year the average number of acute attacks declined from 3·6 to 1·3 and in the second year to less than one. Probenecid with colchicine appeared to be more effective than probenecid alone. Untoward reactions to probenecid, which were recorded in 21 cases, included gastrointestinal disturbances, rashes, headache, pruritus, and polyuria. In two of three cases in which urinary calculi were passed the calculi gave a positive reaction for urates. One patient experienced transient mental confusion. Radiological examination of the bones revealed arrest of the disease in eight cases, including four in which recalcification was observed in punched-out areas. Diminution in the size of the tophi was demonstrated in eighteen of 47 patients who received probenecid for at least 6 months. In three cases the disease failed to respond to treatment.

During the course of the investigation the authors studied the history and development of the disease. The age at onset was usually 35 to 39 years and the average weight of the patients was 37·3 lb. (17 kg.) higher than normal. It is concluded that tophaceous and non-tophaceous gout are clinical variants, and that the presence of renal disease is not essential for the development of tophi. *A. Garland.*

A Little Known Metabolic Disorder in Gouty Subjects: Hyperoxalaemia. (Un trouble humoral méconnu chez le goutteux: l'hyperoxalémie.) MUGLER, A. (1959). *Presse méd.*, **67**, 1309. 29 refs.

Since Garrod first demonstrated (*Trans. med.-chir. Soc. Edinb.*, 1848, **31**, 83) the great increase in the blood uric acid level in gouty patients, this finding has tended to dominate the picture. However, the present author, writing from Vittel, points out that the metabolism of oxalic acid may also be disturbed in gouty subjects. In such patients Loeper and Guillaumin have reported an alteration in the ratio between the blood oxalic acid level and the urinary oxalic acid level to between 2 : 1 and 3·5 : 1, instead of the normal ratio of 1 : 2. In a study of 493 patients with hyperuricaemia the present author found hyperoxalaemia to be present in 395 cases (80 per cent.), a blood oxalic acid level of 0·5 mg. per 100 ml. being taken as the upper limit of normal. Of the 260 patients with obvious clinical gout, 86·5 per cent. had hyperoxalaemia, while in the 233 with hyperuricaemia (but no gout) the incidence was 73 per cent. This finding is considered to be of clinical importance, since a study of lithiasis in eighteen hyperuricaemic subjects (with normal blood levels of oxalic acid) revealed that 67 per cent. of the calculi contained oxalic acid and only 39 per cent. contained uric acid.

Two substances appear to be common to uricaemia and oxalaemia, namely, the aminoacetic acid glycocoll (glycine) and purines. The ingestion of the former has been shown to lead to increased excretion of oxalic acid in subjects prone to oxaluria (but not in normal subjects). Purines also have recently been shown to be associated with increased oxaluria. The author considers that in those cases in which hyperoxalaemia is found to be associated with hyperuricaemia the attacks of gout tend to be aggravated. This, he suggests, may explain the presence of an almost normal blood uric acid level in some gouty subjects in whom the blood oxalic acid level, were it estimated, might be found to be considerably raised. *D. Preiskel.*

Study of the Paradoxical Effects of Salicylate in Low, Intermediate and High Dosage on the Renal Mechanisms for Excretion of Urate in Man. YÜ, T. F., and GUTMAN, A. B. (1959). *J. clin. Invest.*, **38**, 1298. 5 figs, bibl.

Salicylate administered to man in doses of 5 to 6 g. daily increases the urinary excretion of urate, whereas in doses of 1 to 2 g. daily it has the opposite effect. This phenomenon was investigated at the Mount Sinai Hospital (Columbia University College of Physicians and Surgeons), New York, in 23 male gouty subjects. Daily doses of 1, 2, 3, and 5·2 g. acetylsalicylic acid produced changes in the 24-hr urinary excretion of urate of −21, −14, +16, and +37 per cent. respectively. When 5·2 g. sodium bicarbonate was given daily in addition to 5·2 g. aspirin urate excretion was increased by 86 per cent.

Further studies showed that the paradoxical effect was determined at renal tubular level and depended on the concentration of free salicylate in the tubular urine. The conventional view is that urinary urate represents a small fraction of filtered urate that has escaped absorption by the tubules. The authors suggest, however, that the tubules absorb virtually all the urate from the glomerular filtrate and that the urate present in the urine is the product of tubular secretion. It is further postulated that a low concentration of salicylate in the tubular urine depresses the tubular secretion of urate, thus causing a reduction in its excretion. Intermediate concentrations of salicylate in the tubules depress tubular secretion and also, to some extent, tubular absorption of urate, so that the excretion of urate in the glomerular filtrate remains unaltered, while high tubular concentration of salicylate (produced by high dosage of salicylate or smaller doses plus an alkalinizing agent) depress tubular absorption to such an extent that there is an increase in urate excretion over the normal value. The authors suggest that the uricosuric effect of probenecid, which is produced by inhibition of tubular absorption of urate, is counteracted by small doses of salicylate in part because of the suppression of tubular secretion of urate. *G. S. Crockett.*

Radiology of Gout. BRAILSFORD, J. F. (1959). *Brit. J. Radiol.*, **32**, 472. 10 figs, 9 refs.

In this article from the University of Birmingham, the author discusses gout as a constitutional disorder. Whereas the diagnosis may be clear from the presence of tophi, and may be easy, even in their absence, from family and personal history, in some cases the signs and symptoms may lead to confusion with rheumatism. This is especially true when multiple joints are affected and no tophi are found. In such cases radiography, which frequently provides only confirmatory evidence of the diagnosis, may be of particular value.

Characteristically, radiographic changes occur in the extremities where tophi may cause bone dissolution on the joint surface, on the periphery or within the substance of a bone distal to a joint. These do not provoke reactive changes in the surrounding bone and occasionally calcification within these lesions occurs. Destruction may be so great that amputation becomes necessary.

In more proximal joints localized areas of bone destruction may similarly develop and one of these may be the site of presenting symptoms. The author illustrates this by quoting at length the case history of a man of 33 who suffered from sudden and multiple joint pain followed by swelling of the right knee. A false diagnosis of rheumatic fever was not corrected for nearly 2 years when the true diagnosis of gout was prompted by a similar attack affecting the feet. Observation over the subsequent 26 years showed the appearance of numerous destructive lesions, not only in the extremities but also in the knees, ankles, shoulders and elbows. Smaller cyst-like lesions were also noted in a greater trochanter.

[The author regards his report as being supplementary to previous writings on the subject.] *R. O. Murray.*

Anatomical and Clinical Study of Atypical Forms of Gout. (Eine anatomische und klinische studie atypischer gichtforman.) STOIA, I., and STOLA, H. (1959). *Z. Rheumaforsch.*, **18**, 271. 20 refs.

Uricosuric Effect of Certain Oral Anticoagulant Drugs. THOMPSON, G. R., MIKKELSEN, W. M., and WILLIS, P. W. (1959). *Arthr. and Rheum.*, **2**, 383. 5 figs, 20 refs.

Colchicine Analogs in the Treatment of Acute Gout. WALLACE, S. L. (1959). *Arthr. and Rheum.*, **2**, 389. 2 figs, 30 refs.

Favourable Clinical Effect of Co-enzyme A in Certain Cases of Chronic Gout. (Effect clinique favorable du co-enzyme A dans quelques cas de goutte chronique. DHOTEL, Y. (1959). *Thérapie*, **14**, 670.

Pararheumatic (Collagen) Diseases

Antimalarials in Treatment of Sjögren's Syndrome. HEATON, J. M. (1959). *Brit. med. J.*, **1**, 1512. 6 refs.

The trial herein reported of antimalarial drugs in the treatment of Sjögren's syndrome was considered worthwhile because there is evidence that this syndrome is a form of systemic lupus erythematosus, a disease in which antimalarial drugs have a beneficial effect. A total of 25 patients with Sjögren's syndrome were treated at first with chloroquine and later with the reputedly less toxic hydroxychloroquine ("plaquenil"). All the patients had received treatment previously, some for many years, by orthodox methods, but usually there was only slight benefit. The dose of plaquenil was 800 mg. daily for 8 to 12 weeks; if there was improvement the dosage was then reduced to 400 mg. daily. The ocular irritation responded first and then photophobia. Altogether five patients were "greatly improved", twelve were improved, and eight failed to benefit.

The author states that the period for which it is necessary to continue treatment is not known. In four patients the drug was stopped and the eyes became worse within a month, while in one case the eyes remained in a satisfactory state for 3 months after cessation of treatment.

Of 22 patients in the series who had plaquenil, six experienced side-effects; these were of a minor nature and resolved rapidly on reducing the dose or withdrawing the drug. *Kenneth Stone.*

Roentgenologic Evaluation of Systemic Lupus Erythematosus. TAYLOR, T. L., and OSTRUM, H. (1959). *Amer. J. Roentgenol.*, **82**, 95. 8 figs, 32 refs.

(1) The roentgen findings in systemic lupus erythematosus depend on the stage of the disease during which the roentgenograms are taken.

(2) Changes visible in the chest roentgenograms may suggest the correct diagnosis. These changes are:

Initial Acute Stage: Bilateral, moderate, or massive pleural effusion; subpleural inflammation; perivascular inflammation; small areas of interstitial pneumonitis at the lung bases; small areas of segmental pneumonitis at the lung bases.

Resolving Stage: Minimal unilateral or bilateral pleural effusion: minimal to moderate pericardial effusion with straightening of the left border of the cardiac silhouette but without widening of the heart base; small linear areas of "plate-like" atelectasis at the lung bases; areas of segmental atelectasis at the lung bases.

Chronic Stage: Unless the nephrotic syndrome is present, the cardiac contour returns to normal or cor pulmonale develops. In some instances the outline of the pulmonary conus remains partly obscured by fibrosis which fills in the pericardial spaces around the conus. The pleural effusion may completely disappear. Fine pulmonary scars may be seen at the lung bases frequently associated with "tenting" of the pleura, or the lungs may appear clear. Multiple pulmonary infections occur.

Exacerbation: Pleural and pericardial effusions are limited by adhesions; fine linear densities are intermingled with small areas of interstitial pneumonia at the lung bases; basal areas of segmental pneumonitis occur; subpleural and perivascular inflammation is present.

(3) Delayed renal function may be evident on intravenous pyelography.

(4) The relationship between systemic lupus erythematosus and destructive joint changes typical of rheumatoid arthritis is unproved. In the cases of this series, there were no instances of demonstrable joint changes other than soft tissue oedema and those changes attributable to Raynaud's syndrome.—[*Authors' summary.*]

Factors influencing the Course and Prognosis of Systemic Lupus Erythematosus. McCombs, R. P., and Patterson, J. F. (1959). *New Engl. J. Med.*, **260**, 1195. 6 refs.

Up to 1949 the prognosis in systemic lupus erythematosus was very poor, but the introduction of the L.E.-cell test in 1948 and the almost simultaneous introduction of steroid treatment in 1949 made it difficult to compare later series, even directly, with earlier series not treated with steroids because of probable differences in diagnostic criteria. In the present study of 77 cases of systemic lupus erythematosus seen at the New England Center Hospital, Boston, the authors set out to re-examine the course and prognosis of this disease in terms of sex, age, pregnancy, steroid therapy, and certain specific manifestations of the disease process. The analysis included fourteen fatal cases first diagnosed before 1949 on clinical evidence alone or with additional post-mortem evidence; the remaining 63 cases were diagnosed between 1949 and 1958, L.E.-cell tests being performed in twenty fatal cases and on 39 patients still living; the results were not available in four (fatal) cases. The L.E.-cell test was positive in thirteen of the twenty fatal cases and in eleven of the 39 still living patients; in no case, however, was the diagnosis based solely on a positive L.E.-cell test.

There were only eight males in the series, and of these six died compared with 32 out of 69 females. Patients under the age of 21 years at the time of diagnosis did worse (nine out of fifteen died) than those over 45 (five out of fifteen). In some cases, however, symptoms may have been present for some years before the diagnosis was made. As other workers have found, the presence or absence of renal disease was the most important prognostic feature. Steroid treatment seemed to have no effect on renal involvement, but did suppress the rash, fever, serositis, myocarditis, pneumonitis, and haematological and neurological complications. Pregnancy had little effect once the disease was established. The authors suggest that steroid therapy may have prevented the appearance of renal disease, since only one out of 29 patients so treated later developed renal trouble, compared with three out of ten not given steroids. In the untreated series death was due to "toxic" or cardiac causes or to uraemia; in the steroid-treated patients ten out of eighteen died of renal failure and uraemia, while six out of eight died of complications perhaps related to steroid therapy, including infections and gastrointestinal haemorrhage.

[There is a great deal of useful information in this paper which will repay detailed study.]

E. G. L. Bywaters.

Clinical and Roentgenologic Signs of Collagen Diseases Involving the Thorax. Nice, C. M., Menon, A. N. K., and Rigler, L. G. (1959). *Dis. Chest*, **35**, 634. 11 figs.

The authors discuss the clinical, pathological, and radiological findings in 109 patients with collagen diseases admitted to the University of Minnesota Hospitals, Minneapolis, between 1942 and 1956. The aetiology is briefly discussed, and the symptoms at onset, laboratory data, electrocardiographic changes, and response to steroid therapy are analysed in a number of tables. The series included forty cases of polyarteritis nodosa, 37 of disseminated lupus erythematosus, twenty of scleroderma, seven of dermatomyositis, and five of rheumatic pneumonitis. There was pathological confirmation of the diagnosis in over two-thirds of the cases.

The radiological findings are described in some detail. The authors consider that abnormalities occur in the chest during the course of the disease in over 80 per cent. of cases. Interstitial pneumonitis, pleural effusion, and cardiac enlargement were common to all five diseases. Bilateral hilar vascular prominence was most often seen in polyarteritis, while interstitial pulmonary fibrosis and emphysema occurred mainly in scleroderma and dermatomyositis; a honeycomb appearance of the mid- and lower-lung fields was present in 20 per cent. of cases of scleroderma. Cardiac lesions were more common in disseminated lupus erythematosus and rheumatic pneumonitis and small pulmonary nodules in polyarteritis and scleroderma. Abnormal radiological findings in other systems are also briefly discussed and twelve cases illustrating the value of the *x*-ray findings in the differential diagnosis are described in detail.

B. Goldberg.

Methylprednisolone (Medrol) in the Treatment of Systemic Lupus Erythematosus. Dubois, E. L. (1959). *J. Amer. med. Ass.*, **170**, 1537. 10 refs.

The results in forty cases of active systemic lupus erythematosus treated with methylprednisolone ("medrol") over 16 months are reported from the University of Southern California, Los Angeles. In fifteen of these cases antimalarial treatment was given concurrently.

The pattern of response was similar to that obtained with prednisone, triamcinolone, and other anti-inflammatory steroids, while the incidence of moon face, hirsutism, acne, and the formation of striae was about the same. The average daily dose of methylprednisolone for initial suppression was 29·2 mg. (range 8 to 96 mg.) and for maintenance 25·9 mg. per day. There was a high incidence of ecchymosis, which occurred in 27 per cent. of the patients, as compared with 14 per cent. with triamcinolone and 3 per cent. with prednisone. A new peptic ulcer appeared in only one case, which is described. Of the eighteen patients who had received other steroids, only two had better control and felt better while taking methylprednisolone. Nevertheless, this preparation is considered a relatively safe and potent anti-inflammatory agent for the treatment of systemic lupus erythematosus.

Oswald Savage.

Pseudo-Tumour of the Orbit and Polyarteritis Nodosa. WALTON, E. W. (1959). *J. clin. Path.*, **12**, 410. 11 figs, 11 refs.

The report of a case of pseudo-tumour of the orbit which ended fatally. The *post mortem* examination showed evidence of polyarteritis nodosa. The relationship of pseudo-tumour with Wegener's granulomatosis is considered and the aetiology of necrotizing arteritis is discussed. *A. G. Cross.*

Periarteritis Nodosa with Ocular Signs. (À propos d'un cas de périartérite noueuse, avec manifestations oculaires.) GODDÉ-JOLLY, D., and AUBERT, P. (1959). *Bull. Soc. Ophthal. Fr.*, No. 2, 137. 47 refs.

Progressive Systemic Sclerosis-Scleroderma. Experience in 67 Cases. (Esclerosis sistemica progresiva-esclerodermia. Experiencia sobre 67 casos.) GONZALEZ, A. (1959). *Rev. med. Chile*, **87**, 498. 13 figs, bibl.

P-Toluene Sulphonic Acid Test for Systemic Lupus Erythematosus. BARKOFF, J. R., and SAWYER, F. (1959). *A.M.A. Arch. Derm.*, **80**, 445. 6 refs.

Neurological Syndromes in Lupus Erythematosis. (Über neurologische syndrome im rahmen des lupus erythematodes.) FUHRMANN, W., and NAWROTZKI, J. (1959). *Dtsch. Z. Nervenheilk.*, **179**, 444. 3 figs, 41 refs.

Intermediary Metabolism of Phenylalanine and Tyrosine in Diffuse Collagen Diseases. II. Influences of the Low Phenylalanine and Tyrosine Diet upon Patients with Collagen Disease. NISHIMURA, N., OKAMOTO, H., YASUI, M., MAEDA, K., and OGURA, K. (1959). *A.M.A. Arch. Der.*, **80**, 466. 3 figs, 49 refs.

Incidence of Malignant Tumours in Dermatomyositis and Other Collagen Diseases. (La fréquence des tumeurs malignes dans la dermato-myosite et les autres collegénoses.) BERTHOUD, E., and MARTIN, E. (1959). *Schweiz. med. Wschr.*, **89**, 953. 32 refs.

Pleuropulmonary Manifestations in Lupus Erythematosus Disseminatus. MYHRE, J. R. (1959). *Acta med. scand.*, **165**, 55. 4 figs, 15 refs.

Clinical Experience with the L.E.-cell Test. (Klinische Erfahrungen bei Untersuchung der Lupus Erythematosus /L.E.-/Zelle.) BENCZE, G. (1959). *Acta med. scand.*, **165**, 287. 5 figs, 20 refs.

Colon in Systemic Sclerosis (Scleroderma). MESZAROS, W. T. (1959). *Amer. J. Roentgenol.*, **82**, 1000. 4 figs, 7 refs.

Digestive Symptomatology of the Collagen Diseases. (Sintomatologia digestiva delle collagenopatie.) RIZZI, D. (1959). *Settim. med.*, **47**, 439. 2 figs, 33 refs.

Collagen Diseases with Special Reference to Atypical and Abdominal Forms. (Considérations sur les collagenoses, spécialement les formes atypiques et abdominales.) STOIA, I. (1959). *Rev. argent. Reum.*, **24**, 234.

Heart in Systemic Lupus Erythematosus. [Review article.] SHEARN, M. A. (1959). *Amer. Heart J.*, **58**, 452. Bibl.

General Pathology

Relationship of Sialic Acid and C-reactive Protein Levels in Human Serum. TURUMI, K.-I., HAMAGAMI, L. T., and KENKEL, H. (1959). *J. Amer. med. Ass.*, **170**, 2160. 2 figs, 8 refs.

Investigations are reported from the Institutum Divi Thomae and St. Mary's Hospital, Cincinnati, in which the authors sought to find an absolute correlation between the amounts of two acute-phase reactants in the serum—C-reactive protein (determined by the capillary precipitin method) and protein-bound sialic acid (determined by the method by Böhm and others; *Klin. Wschr.*, 1954, **32**, 289). Sera were examined for both factors from 58 subjects, including fifteen normal blood donors. No definite correlation was found between the levels of the two factors, although there was some degree of relationship [both being increased as a normal reaction to inflammatory processes]. The maximum sialic acid value of serum negative for C-reactive protein was 210 mg. per decilitre, and only four of 34 sera positive for C-reactive protein showed sialic acid values less than 210 mg. per decilitre. The mean value for sialic acid in normal serum was 130 ± 7 mg., in sera negative for C-reactive protein 143 ± 7 mg., and in sera positive for C-reactive protein 259 ± 12 mg. per decilitre. It is considered "likely that different pathological processes may account for the appearance of C-reactive protein and an increase in the serum sialic acid level".

[The greater part of the serum hexosamine-pyruvate compound known as neuraminic or sialic acid is bound to the α-seromucoid fraction of the protein or the Winzler fraction soluble in 1·8 M perchloric acid. The C-reactive protein is generally held to be in the γ-globulin fraction, although it has been reported to be an α globulin. The normal values for serum sialic acid given in this paper are double those quoted by the authors of the method utilized. Considering the wide variations found in different diseases in both the γ-globulin and α-seromucoid fractions, it would seem unlikely to expect any absolute correlation between these two estimations in pathological sera.] *Harry Coke.*

Diphenylamine Reaction in Rheumatism and Non-specific Infective Polyarthritis. [In Russian.] TIHONRAVOV, V. A. (1959). *Klin. Med. (Mosk.)*, **37**, 41. 6 refs.

Destruction of connective tissue leads to the accumulation in the blood of mucoproteins, which can be detected in the serum by means of the diphenylamine reaction. The author, using the colorimetric modification of this reaction described by Ayala and others (*J. clin. Invest.*,

1951, **30**, 781), examined the serum of ten healthy persons, 96 patients suffering from "rheumatism", and 86 patients suffering from non-specific infective polyarthritis. Statistical evaluation of the results showed that in both groups of patients the values obtained, measured in extraction units, were significantly higher than in the control group and that the intensity of the diphenylamine reaction was closely related to the activity and severity of the disease process. *F. S. Freisinger.*

Effect of Sequestrene and Heparin on the Erythrocyte Sedimentation Rate. DENSON, K. W. (1959). *J. clin. Path.*, **12**, 262. 14 refs.

By careful statistical analysis of triplicate estimations the author, in an investigation at University College Hospital, London, has shown that when used alone the anticoagulant sequestrene, like heparin and oxalate, is unreliable for determining the erythrocyte sedimentation rate (E.S.R.). However, blood which has been collected into oxalate, heparin, or sequestrene and subsequently [maximum interval not determined] diluted with one-fourth its volume of 3·8 per cent. sodium citrate is suitable for determining the E.S.R. by the Westergren method. *M. Sandler.*

Use of a Sequestrene-Citrate Mixture in the Estimation of the Blood Sedimentation Rate. MELVILLE, I. D., and RIFKIND, B. M. (1959). *J. clin. Path.*, **12**, 258. 24 refs.

The retardation of the erythrocyte sedimentation rate (E.S.R.) in blood which has been stored is believed to be related to the anticoagulant used and the temperature at which the blood is stored. If, however, 1 mg. sequestrene is used as the anticoagulant, blood stored at 5° to 10° C. for 24 hours can still be used for estimation of the E.S.R. by Westergren's method, provided it is then mixed with a 3·8 per cent. solution of sodium citrate in the proportion of four parts of blood to one of citrate. At Glasgow Royal Infirmary the E.S.R. (Westergren) of 25 samples of fresh blood-citrate mixture was compared with that of a similar number of samples of fresh blood-sequestrene-citrate mixture. No significant difference was observed between the E.S.R. of the two mixtures, nor was there any appreciable difference, with the blood-sequestrene-citrate technique, between the E.S.R.s of 25 samples of fresh blood and 25 samples which had been stored for 24 hours.

[This finding promises to extend widely the use of the E.S.R. in clinical practice.] *M. Sandler.*

Observations on the Precipitation Test for Diagnosis of Systemic Lupus Erythematosus. SYLVESTER, R. L., SLUKA, G. J., KANABROCKI, E. L., and RUBNITZ, M. E. (1959). *Amer. J. clin. Path.*, **32**, 45. 14 refs.

Specimens of serum from 3,652 patients were tested with *p*-toluenesulphonic acid. There were 23 false positive reactions and one false negative, the latter in a patient with classic findings of systemic lupus erythematosus at necropsy. None of the patients in the false positive group had any clinical or pathologic findings of systemic lupus erythematosus.

The factor responsible for precipitation in the false positive reactions was observed to be in the beta globulin fraction.—[*From authors' summary.*]

Detection of Rheumatoid Factor(s) by Means of Photoelectric Measurement without Hemagglutination. COHEN, E., NETTER, E., and NORCROSS, B. M. (1959). *Amer. J. clin. Path.*, **31**, 507. 1 fig., 22 refs.

The F.II agglutination and the F.II precipitation reaction of Epstein and others (*Proc. Soc. exp. Biol. (N.Y.)*, 1956, **91**, 235) are based on the interaction between γ globulin (Cohn Fraction II) and the rheumatoid factor macroglobulin. This reaction may be enhanced by preheating the F.II globulin reactant to 63° C. for 10 minutes. This paper from Roswell Park Memorial Institute, Buffalo, New York, records the estimation of the induced turbidity of this reaction by means of a photronreflectometer. The results were correlated with those of the alligator erythrocyte agglutination and the standard Rose-Waaler haemagglutination reactions.

A total of 58 sera were examined. All of fifteen cases of rheumatoid arthritis, in which the haemagglutination reactions were positive, showed increased precipitation activity (turbidity), whereas negative results were obtained in both tests with sera from 26 normal donors and from fifteen patients with various other rheumatic and allied diseases, which included dermatomyositis (1) and lupus erythematosus (3), and from two with multiple myeloma. Sera from two cases of macroglobulinaemia gave negative turbidity reactions with positive haemagglutination reactions. Apart from these cases, representing 3·4 per cent., no false positive results were obtained.

Harry Coke.

Latex-Fixation Test in Rheumatoid Arthritis. I. Clinical Significance of a Thermolabile Inhibitor. SCHUBART, A. F., COHEN, A. S., and CALKINS, E. (1959). *New Engl. J. Med.*, **261**, 363. 1 fig., 19 refs.

The replacement of sheep erythrocytes in agglutination reactions based on the techniques of Rose and Waaler by polystyrene particles in the technique outlined by Singer and Plotz eliminated the need to heat the serum to destroy complement. In this paper from Harvard Medical School and the Massachusetts General Hospital, Boston, it is demonstrated that this preliminary heating to 56° C. for 30 minutes also destroys the action of a thermolabile inhibitor of the agglutination phenomenon. Thus, when a native unheated serum is used in the standard technique of Singer and Plotz (F.II L.P. test) a prozone will occur in the lower dilutions of the series, where agglutination is inhibited. In 25 of 177 "definite" cases of rheumatoid arthritis total inhibition was observed with native serum, whereas after preliminary heat inactivation titres as high as 1 : 5,120 were determined. The thermolabile inhibitor may be demonstrated in any serum that has agglutinating activity in the F.II L.P. test. Of the 177 sera from patients with "definite" rheumatoid arthritis, 118 (66·6 per cent.) gave positive results (1 : 160 or higher) after preliminary heat inactivation, whereas only 93 (52·5 per cent.) of the unheated aliquots gave positive results, 38 of the 93 showing the

prozone phenomenon. Tests were performed with heated and unheated serum from 418 patients from an arthritis clinic (including the 177 mentioned above), twenty patients with leprosy, and 360 patients (including normal subjects) from a general medical clinic and gave similar results. This thermolabile inhibitory factor has some of the characteristics of serum complement.

[It is to be remembered in considering this phenomenon that whether or not the serum is heat-inactivated before testing, the technique of the test involves heating the mixed reactants to 56° C. for 2 hours.] *Harry Coke.*

Clinical Research on the "Rheumatoid Factor". (Ricerche cliniche sul "fattore reumatoide".) GIORDANO, M., ARA, M., and DRAMMIS, E. (1959). *Rif. med.*, **73**, 783. 11 refs.

In this paper from the Medical Clinic of the University of Naples the authors first review the evolution of the various tests for the detection of the rheumatoid factor in human serum. They then report their own experience with the "R.A." test, a modification of the latex fixation test of Singer and Plotz, in thirty cases of rheumatoid arthritis three of ankylosing spondylitis, forty of painful osteo-arthritis, and 188 of non-rheumatic disease, including 133 cases of diabetes, and five of Addison's disease. The result of the test was positive in 96·7 per cent. of cases of rheumatoid arthritis, whereas in acute rheumatism it was positive in 2 per cent. of cases only. On the other hand positive results were obtained in 25 per cent. of the cases of painful osteo-arthritis, in 27·7 per cent. of the cases of diabetes, and in four of the five cases of Addison's disease. The authors conclude that the R.A. test is useful in the diagnosis of rheumatoid arthritis, though the possibility of false positive reactions has to be borne in mind, especially in cases of painful osteo-arthritis, in which the problem of differential diagnosis often arises. The R.A. test is slightly more sensitive and is easier to carry out than the Rose-Waaler test. *E. Forrai.*

Changes in the Serum Protein Fractions in Acute Rheumatism. [In Russian.] TROFIMOVA, T. M. (1959). *Klin. Med.* (*Mosk.*), **37**, 45.

A reduction in the albumin fraction of the serum protein and an increase in the α- and γ-globulin fractions occur in cases of acute rheumatism. The increase in the α globulins is most closely related to the activity of the rheumatic process, though in general the changes in the blood protein fractions seem to go parallel with the clinical symptoms. According to the author these changes depend not only on the activity of the rheumatic process, but also on the degree of circulatory disorder. *F. S. Freisinger.*

Estimation of Polysaccharides in the Serum of Patients Suffering from Acute Rheumatism. [In Russian.] HRAMOV, V. M. (1959). *Klin. Med.* (*Mosk.*), **37**, 48. 5 refs.

A new method of estimating the polysaccharide content of the serum by digestion with pancreatin and extraction with toluene was used in the investigation of 54 patients suffering from acute rheumatism and subacute bacterial endocarditis. In both conditions a significant increase in the serum polysaccharide level was found which, it is claimed, provides an index of the activity of the rheumatic process and of the efficacy of treatment in cases such as these. *F. S. Freisinger.*

Estimation of Fibrin in the Plasma in Rheumatism. [In Russian.] VOROBOREVA, A. I. (1959). *Klin. Med.* (*Mosk.*), **37**, 50. 7 refs.

The fibrin content of the plasma of 144 rheumatic subjects, including 78 suffering from an acute attack, was estimated by the method of Wohlisch (*Ergebn. Physiol.*, 1940, **43**, 174). Healthy subjects and patients suffering from uncomplicated chronic tonsillitis served as controls. Most of the patients with acute rheumatism had an increased plasma fibrin level, the average value being 16·2 mg. per ml. compared with 6 to 11 mg. per ml. in the control group. It is claimed that this investigation is of diagnostic value. *F. S. Freisinger.*

Serological Investigations in Rheumatic Eye Diseases. (Serologische Untersuchungen bei rheumatischen Augenerkrankungen.) DIECKHUES, B., CONRADS, H., and WAGNER, K. (1959). *Klin. Mbl. Augenheilk.*, **135**, 516.

The authors used three serum tests:

(1) Antistreptolysin reaction—an antigen-antibody reaction with streptolysin of *Streptococcus haemolyticus*.
(2) Waaler-Rose test—agglutination of sensitized erythrocytes.
(3) The latex test—a modification of the above, using a colloid suspension of latex rubber particles instead of erythrocytes.

82 clinically suspicious cases of rheumatic aetiology were studied. Only a small fraction of the results was positive. The slightness of the ocular lesions and the low virulence may explain those findings. *J. L. Reis.*

Appraisal of the Latex Test for Rheumatoid Arthritis. JEFFREY, M. R. (1959). *J. Lab. clin. Med.*, **54**, 525. 19 refs.

Studies of Polyarthritis and Other Lesions induced in Rats by Injection of Mycobacterial Adjuvant. I. General Clinical and Pathologic Characteristics and Some Modifying Factors. PEARSON, C. M., and WOOD, F. D. (1959). *Arthr. and Rheum.*, **2**, 440. 16 figs, 15 refs.

On Muscle Cells, Aschoff Bodies, and Cardiac Failure in Rheumatic Heart Disease. MURPHY, G. E. (1959). *Bull. N.Y. Acad. Med.*, **35**, 619. 8 figs, bibl.

Intrinsic Viscosity of Hyaluronic Acid Synthesized in Tissue Culture in the Presence of Normal and Rheumatoid Arthritic Serum Respectively. HEDBERG, H., and MORITZ, U. (1959). *Acta rheum. scand.*, **5**, 169. 3 figs, 11 refs.

Methods for Isolation and Identification of Acid Mucopolysaccharides in Connective Tissue. ZACHARIAE, F., and DYRBYE, M. O. (1959). *Acta rheum. scand.*, **5**, 190. 1 fig., bibl.

Serum Mucoproteins in Inflammatory Rheumatism. (Mucoproteinas sericas en los reumatismos de naturaleza inflamatoria.) CONTRERAS, V., MORALES, J., and BARAONA, E. (1959). *Arch. argent. Reum.*, **22**, 46. 6 figs, 27 refs.

Effect of Age and Heat on Human Collagenous Tissue. Studies on Acid Solubility, Titration Curves, and Elasticity. KOHN, R. R., and ROLLERSON, E. (1959). *A.M.A. Arch. Path.*, **68**, 316. 12 refs.

Contribution to the Question of the Specificity of the Lupus Erythematosus Precipitation Test of Jones and Thompson. (Beitrag zur Frage der Spezifität des Lupus erythematodes-Praecipitations-Tests von Jones und Thompson.) HOMBURG, M., and SCHMIDT, H. (1959). *Med. Mschr.*, **13**, 779. 4 refs.

Paper Electrophoresis of Knee-joint Effusions. (Papierelektrophorese bei Kniegelenksergüssen.) KINDLER, H. (1959). *Dtsch. med. Wschr.*, **84**, 2192. 7 figs, 12 refs.

Value of Mucoprotein Levels and Other Serological Reactions in Rheumatoid Arthritis. FELDMAN, C., HESS, E. V., and MARKHAM, R. L. (1959). *Ann. phys. Med.* **5**, 113. 6 figs, 8 refs.

Unstable Inhibitory Mechanism in Rheumatoid Sera. MEISELAS, L. E., and PORUSH, J. (1959). *Proc. Soc. exp. Biol. (N.Y.)*, **102**, 61. 7 refs.

Physico-Chemical Investigation of Synovial Fluid. FLETCHER, E. D. T. (1959). *Rheumatism*, **15**, 78.

Comparative Study of Certain Serological Reactions in Chronic Articular Rheumatism. (Een vergelijkend onderzoek naar de betekenis van enige serolische reacties bij chronisch gewrichtsreuma). DE BLÉCOURT, J. J., PONDMAN, A., and WESTENDORP BOERMA, F. (1959). *Ned. T. Geneesk*, **103**, 2302. 5 refs.

Plasma Protein Electrophoresis in the Collagen Diseases. (L'électrophorèse des protéines plasmatiques dans les collagénoses.) LEBACQ, E., TIRZMALIS, A., and GOSSART, J. (1959). *Acta gastro-ent. belg.*, **22**, 544. 20 refs.

Results with the Latex-Fixation Test. (Resultaten met de latex-fixatie-proef.) VALKENBURG, H. A., and DE MOS, A. M. (1959). *Ned. T. Geneesk*, **103**, 2305. 23 refs.

Changes in the Serum Proteins in Patients with Rheumatoid Arthritis during Treatment with Prednisolone and Dexamethasone. (Il comportamento delle proteine sieriche in informi affetti da poliartrite cronica primaria in corso di trattamento con prednisolone e desametasone.) ODOARDI, G. B., RAMBALDI, M., and TIRRI, G. (1959). *Rif. med.*, **73**, 1410. 39 refs.

Joint Fluids of Atypical or Unexpected Cytology. "Inflammatory" Effusions in Osteo-Arthritis. Chronic Mononuclear Synovitis. (Épanchements articulaires à cytologie atypique ou imprévue. Poussées "inflammatoires" dans les arthroses. Synovites chroniques à mononucléaires.) ARLET, J., FICAT, P., and VINEL, P. (1959). *Rev. Rhum.*, **26**, 512. 3 figs, 7 refs.

Relation between Blood Sugar and Serum Tryptophane Levels in Rheumatoid Arthritis. (Über den Zusammenhang zwischen dem Blutzucker und Serumtryptophen bei chronischer Polyarthritis.) GÁSPÁRDY, G., and VIDA, M. (1959). *Z. Rheumaforsch.*, **18**, 451. 18 refs.

ACTH, Cortisone, and Other Steroids

Functional Zonation of the Adrenal Cortex. I. Pathways of Corticosteroid Biogenesis. STACHENKO, J., and GIROUD, C. J. P. (1959). *Endocrinology*, **64**, 730. 3 figs, 29 refs.

II. Site of ACTH Action. STACHENKO, J., and GIROUD, C. J. P. (1959). *Endocrinology*, **64**, 743. 22 refs.

These two papers from the Children's Hospital and McGill University, Montreal, report investigations into the production of corticosteroids by the different cellular zones of the mammalian adrenal cortex *in vitro*. The tissue studied was obtained from fresh beef adrenal glands, in which there is a line of pigmented cells along the inner border of the glomerular zone which is visible to the naked eye and allows the zone to be sliced off the rest of the cortex. The reticular zone is poorly differentiated from the fascicular zone and, as preliminary studies showed these two zones to be indistinguishable in behaviour, they were not separated in the main experiments. [The combined fascicular and reticular tissue is referred to as fascicular tissue in this abstract.] Slices of glomerular and fascicular tissue weighing 1·5 to 4 g. were incubated separately for 2 hours in a Krebs-Ringer-bicarbonate medium with added glucose in an atmosphere of 95 per cent. oxygen and 5 per cent. carbon dioxide. Steroid precursors were added to this medium in some experiments (reported in the first paper) and corticotrophin (ACTH) in others (reported in the second paper). After incubation the medium was collected and extracted with chloroform. This crude lipid extract was analysed for total $\triangle^4$-3-ketosteroids by the absorption at 2,400 Å, for total α-ketonic reducing steroids by the blue tetrazolium reaction, and for dihydroxyacetone steroids by the Porter-Silber reaction. The crude extracts were then subjected to various chromatographic procedures for the detection of aldosterone, corticosterone, and cortisol and the eluates measured spectrophotometrically. Aldosterone was also assayed biologically.

After incubation without the addition of steroids or corticotrophin the medium from fascicular tissue contained 10 times as much Porter-Silber chromogen as that from glomerular tissue, but salt-retaining activity was confined to the medium from glomerular tissue. Aldosterone was present only in the medium from glomerular tissue, and cortisol only in the medium from fascicular tissue. (The presence of traces of cor-

tisol in the medium from glomerular tissue were attributable to contamination of the tissue slices with cells from the fascicular tissue.) Corticosterone was present in the medium from both types of tissue. Other unidentified steroids were present—one of these was probably 11-dehydrocorticosterone and was present in both media. The addition of progesterone, corticosterone, or deoxycorticosterone to the medium increased the production of aldosterone by glomerular tissue to an equal extent and in proportion to the amount of precursor added. Cortisol production by fascicular tissue was increased by the addition of progesterone or deoxycorticosterone, but not by the addition of corticosterone. Corticosterone production by both types of tissue was increased by the addition of progesterone or deoxycorticosterone. In the presence of 17-hydroxyprogesterone or 17-hydroxy-11-deoxycorticosterone cortisol production occurred in glomerular tissue and was increased in fascicular tissue; this shows that 17-hydroxy precursors can be 21- and 11-hydroxylated by glomerular tissue. On the basis of these findings the authors suggest that though there may be common precursors for different types of cortical steroid, the enzymic mechanisms may differ in the different zones. Thus 17-hydroxylase activity may be confined to the fascicular and reticular zones and 18-oxygenation activity to the glomerular zone. Other enzymic activities (such as 3-β-dehydrogenase and 11- and 21-hydroxylation activities) appear to be common to all zones.

The addition of corticotrophin to the medium increased cortisol production by fascicular tissue, but did not affect aldosterone production by the glomerular tissue. Equivocal results were obtained in respect of corticosterone production, which was possibly increased in both types of tissue. However, in these experiments incubation was continued for 4 hours and there was evidence that corticosterone was disappearing from the medium in the later stages of this period. Similar results were obtained with various corticotrophin peptide preparations. Thus, while no evidence was obtained that corticotrophin influences aldosterone production in any way, it is still possible that it affects corticosterone production in all zones of the cortex.

Aldosterone production by glomerular tissue was increased in the presence of 21-hydroxypregnenolone or progesterone, but not in the presence of cholesterol; none of these effects was altered by the additional presence of corticotrophin. Cortisol production by the fascicular tissue was slightly enhanced in the presence of cholesterol, and very much enhanced in the presence of cholesterol plus corticotrophin; it was also greatly enhanced by the addition of progesterone, and this increase was uninfluenced by the further addition of corticotrophin. *Peter C. Williams.*

Value of Simple Laboratory Procedures in the Diagnosis of Cushing's Syndrome. MAHER, J. F., HERNDON, E. G., and KYLE, L. H. (1959). *Amer. J. med. Sci.*, **237**, 590. 3 figs, 25 refs.

In twenty confirmed cases of Cushing's syndrome occurring in sixteen female and four male patients studied at Georgetown University Hospital, Washington, D.C., the simple haematological tests carried out were evaluated by two standards:

(1) By strict criteria, in which the test results were considered significantly abnormal if the proportion of neutrophil granulocytes exceeded 80 per cent., the total eosinophil granulocyte count was below 40 per c.mm., and the haematocrit value exceeded the normal by at least 5 per cent.; by this standard ten patients showed a significant rise in the number of neutrophils, ten had eosinopenia, and five polycythaemia, fifteen of the twenty patients having one or more of these abnormalities.

(2) By the less strict standard—that is, proportion of neutrophils 70 per cent. or more, eosinophils 80 per c.mm. or less and haematocrit value 3 per cent. above normal—the number of positive test results increased, sixteen patients now showing elevation of neutrophils, seventeen eosinopenia, and twelve (all female) polycythaemia; all the patients showed at least one of these abnormalities and nineteen of them two or more.

Osteoporosis was present in twelve patients and a similar number had significant hypertension (blood pressure above 160/110 mm. Hg), while overt diabetes or carbohydrate intolerance was found in fourteen patients, all the patients showing one or more of these three abnormalities. These findings are compared with those reported in the literature and with the effects of administering corticotrophin and corticosteroids. The authors conclude that careful evaluation of the results of these simple tests is a help in the diagnosis of Cushing's syndrome. *J. Warwick Buckler.*

Cushing's Syndrome: Clinical Differential Diagnosis and Complications. HURXTHAL, L. M., and O'SULLIVAN, J. B. (1959). *Ann. intern. Med.*, **51**, 1. 26 refs.

As Cushing's syndrome is a potentially fatal condition, and since recent advances in the management of the disease have considerably improved the prognosis, its early recognition is of great importance. The present authors have therefore re-examined the early symptoms and problems of diagnosis in a series of 34 cases seen at the Lahey Clinic, Boston. There were 27 female patients and seven males. In 27 cases the diagnosis was confirmed surgically and in seven it was based on characteristic clinical signs and laboratory findings. The clinical onset was rapid in 24 cases, five being of such clear-cut, remittent character that the onset might be termed "episodic"; in the remaining ten cases it was gradual. There were no aetiological differences between these two groups, both containing examples of adrenocortical hyperplasia, adrenocortical adenoma, and aberrant adrenal tissue in the pancreas. In those with a rapid onset the common initial symptoms were oedema of the face and legs, rapid gain of weight, amenorrhoea (which might or might not be associated with either of the preceding features), renal colic, physical weakness, and

mental disturbances. The differential diagnoses that had been considered in these cases were hypothyroidism (7), hyperthyroidism (3), nephritis or nephrosis, cardiac oedema, allergy, simple obesity, idiopathic renal calculi, collagen disease, and psychosis. Facial oedema was present in fourteen cases and, it is suggested, is probably attributable to a combination of factors including the tendency to hypoproteinaemia, hypernatraemia, and vascular fragility. In the cases of gradual onset a more gradual weight gain, oligomenorrhoea and hirsutism, diabetes mellitus, hypertension, mental disturbances, and osteoporosis were common presenting features which made the differential diagnosis from the other causes of such manifestations difficult. Among the helpful pointers to the diagnosis in such cases are the combined appearance of signs, high haemoglobulin level, leucocytosis with relative lymphopenia and eosinopenia, severe fatigue and weakness, nervous complaints, and development of "moon face".

The authors differentiate those features which should be regarded as signs—for example, hypertension (88 per cent.) and osteoporosis (53 per cent.)—from those which are complications, such as pathological fractures (32 per cent.), and renal calculi (30 per cent.). They discuss the cardiovascular complications which may result from the hypertension and the susceptibility of patients with Cushing's syndrome to infection. Three of their patients developed duodenal ulceration, and three others peripheral neuritis of the Guillain-Barré type. They suggest that the latter may be a direct result of the disease process.

B.M. Ansell.

Dexamethasone. HART, F. D., GOLDING, J. R., and BROWN, G. (1959). *Lancet*, **2**, 255. 23 refs.

This paper from the Westminster Hospital, London, records a clinical comparison of the new steroid dexamethasone with its predecessors. In dexamethasone the hydroxyl group of the triamcinolone molecule has been replaced by a methyl group, which appears to have much enhanced its glucocorticoid effect. Dexamethasone was compared with the steroid previously administered (prednisolone in all cases, but two) in thirty cases of rheumatoid arthritis, 1 mg. dexamethasone replacing 5 mg. prednisolone. The new steroid was given for periods varying from 1 to 24 weeks. The 1 : 5 ratio is probably slightly in favour of dexamethasone, the true ratio being perhaps 1 : 6 or 1 : 7. Dexamethasone was considered superior if improvement occurred on changing to it and deterioration on returning to the previous compound. Improvement was judged by the patient's own assessment, strength of grip, and finger swelling as measured by jeweller's rings.

Little difference was apparent: of the thirty patients twelve preferred dexamethasone, twelve prednisolone, and six were indifferent. Dyspeptic symptoms were no less common with dexamethasone than with prednisolone. There would seem to be no obvious advantage in changing to dexamethasone in the treatment of rheumatoid arthritis, though some patients seemed to prefer it. The fact that much the same clinical effect was obtained with a smaller dose is, the authors point out, of little practical importance unless the cost is reduced in the same ratio. One patient with ankylosing spondylitis who had received prednisolone for 16 months improved and became symptom-free when a change to dexamethasone was made. However, in three cases of systemic lupus erythematosus, two of scleroderma, one of ulcerative colitis, and one of status asthmaticus, little or no difference was noted.

Kenneth Stone.

Hyperadrenocorticism (Cushing's Disease): a Study of Surgically Resected Adrenal Glands. COHEN, R. B., CHAPMAN, W. B., and CASTLEMAN, B. (1959). *Amer. J. Path.*, **35**, 537. 14 figs, 21 refs.

From the Massachusetts General Hospital and Harvard Medical School, Boston, a histological study is reported of the adrenal cortex in eighteen female and two male patients aged 16 to 42 years with Cushing's syndrome, biopsy specimens of the adrenal glands from fourteen patients without evidence of endocrine disease serving as controls. The tissue was placed in 10 per cent. buffered formalin and paraffin sections were stained with haematoxylin and eosin, while frozen sections were treated by several methods—for example, they were stained with Sudan IV or subjected to the Schultze, Windaus, Schiff, and naphthoic acid hydrazide tests. In four of the patients the glands were normal on gross examination in twelve the cortex was hyperplastic, and in the remaining four the cortex was adenomatous. In the hyperplastic specimens there was a marked increase in width of the zona fasciculata, but no increase initially in the weight of the gland. Additional signs of overactivity were a depletion of sudanophilic material and cellular atypism.

A. Wynn Williams.

Symptomatology resulting from Withdrawal of Steroid Hormone Therapy. GOOD, T. A., BENTON, J. W., and KELLEY, V. C. (1959). *Arthr. and Rheum.*, **2**, 299. 8 figs, 26 refs.

Writing from the University of Utah School of Medicine, Salt Lake City, the authors point out the several differential patterns of symptoms which may result from the too sudden withdrawal of steroid therapy as seen in young patients at their Pediatric Department, four cases illustrating these different patterns being described in detail. The first was in a girl aged 4 with juvenile rheumatoid arthritis who had been treated initially with cortisone and antibiotics with good results. When fever and joint pain recurred after the withdrawal of cortisone she was given ACTH and cortisone with fair response. When these were discontinued, however, the patient showed a fluctuating temperature, with joint involvement and adenopathy, and the dose of cortisone had to be pushed to 100 mg. daily if the recurrence of the fever was to be prevented. Her symptoms responded to 25 units of ACTH injected four times daily.

The second case was one of bullous exfoliative dermatitis (Stevens-Johnson syndrome) in a 3-year-old boy. The condition responded to intravenous injections of

300 mg. cortisone and 400 mg. tetracycline daily at first. When this was reduced on the 4th day the symptoms recurred and prednisolone, 12 mg. orally, was substituted. The patient collapsed and died within 24 hours of the change. The interesting finding *post mortem* was a massive haemorrhagic lesion in the left adrenal gland.

The third case, illustrating the symptoms of pseudo-rheumatism and Addisonian-like crisis, occurred in a boy aged 6 with juvenile rheumatoid arthritis who had been receiving corticosteroid therapy for 4 years with only occasional flare-ups. Before admission he had vomited and steroid therapy was withdrawn. In hospital he was restless and irritable, and any movement caused pain. The blood sodium and potassium levels were dangerously low and the electrocardiogram was typical of electrolyte deficiency. He recovered after the intravenous administration of cortisone and electrolytes.

The last case was one of juvenile rheumatoid arthritis in a child aged 3 in whom an intravenous dose of 1 mg. hydrocortisone per lb. (2·2 mg. per kg.) body weight was followed after 12 hours by acute symptoms, which were relieved by oral prednisolone.

In a special test twenty healthy adult volunteers were given hydrocortisone intravenously or prednisolone orally or intravenously and the blood steroid levels determined. In completing a questionary many of these subjects recorded "rheumatic" symptoms 4 to 72 hours afterwards. These were shown to occur when the plasma steroid levels were decreasing and were not dependent on the absolute steroid level. Discussing the origin of lesions in acute cases the authors compare the haemorrhagic necrosis of the adrenal gland to that of the uterine mucosa during menstruation, and suggest that both represent endocrine withdrawal phenomena of the same nature. In the treatment of withdrawal symptoms they consider that the dosage of steroids should be increased and not diminished in such cases.

William Hughes.

Dexamethasone Acetate. A Study of its Clinical and Biological Effects. (Étude des effets cliniques et biologiques de l'acétate de déxaméthasone.) TURON and GIACARDY (1959). *Presse méd.*, **67**, 1977. 1 fig., 27 refs.

Other General Subjects

Bone Lesions of Childhood Leukaemia: a Survey of 140 Cases. WILLSON, J. K. V. (1959). *Radiology*, 72, 672. 8 figs, 18 refs.

The diagnostic value in leukaemia in childhood of lesions of the long bones was studied in 140 cases seen at Johns Hopkins Hospital, Baltimore. Radiologically, bone changes were present in 89 (64 per cent.) of the patients, 74 of whom, predominantly males and white children, were between 2 and 10 years of age. Extensive destructive lesions were observed, which on the whole presented a characteristic pattern, with areas of rapid bone growth being peculiarly liable to involvement. Metaphysial bands of translucency were the most common finding (76 cases) and were usually seen at the knees and wrists. Of 740 consecutive radiographs of the long bones obtained over a period of one year 32 revealed this transverse translucent line of the metaphyses; none of the 32 patients had leukaemia and only four were over 2 years of age. The author therefore considers that this finding is non-specific below that age. In leukaemia, unlike scurvy, the lateral cortical margins and the metaphysial plates are usually intact. In 53 cases osteolytic lesions were found in the spongiosa of the long bones, varying from punctate areas of increased translucency to zones of frank destruction. In some cases extensive areas of metaphysial decalcification may suggest that the metaphysial band has expanded to include the spongiosa. In three cases infractions of such areas were noted. Pathologically, these destructive lesions are attributed to interference with nutrition and pressure by the proliferating leukaemic tissue, with increased osteolysis. Periosteal elevation along the shafts of the long bones, due to leukaemic infiltration between the cortex and the periosteum, was evident in 27 cases. Radiographs of the long bones in cases resembling leukaemia clinically, including 25 of rheumatoid arthritis and twenty of anaemia, did not show the transverse translucent line at the metaphysis, the osteolytic lesions, or the periosteal elevation seen in leukaemia. In metastatic neuroblastoma the radiological picture may be comparable, but without the transverse metaphysial band of translucency and with a greater tendency to central, rather than peripheral, bone involvement. The author concludes that radiographs of the long bones may be of value when leukaemia is suspected, especially in patients over the age of 2 years. *R. O. Murray.*

Ann. Rheum. Dis. (1960), **19**, 95.

GOLD THERAPY IN RHEUMATOID ARTHRITIS

REPORT OF A MULTI-CENTRE CONTROLLED TRIAL

ARRANGED BY

THE RESEARCH SUB-COMMITTEE OF THE EMPIRE RHEUMATISM COUNCIL*

(1) Introduction

In 1938 Sir Stanley Davidson, then the Chairman of the Scientific Advisory Committee of the Empire Rheumatism Council (E.R.C.), made plans for a "double-blind" controlled trial of gold salts in the treatment of rheumatoid arthritis. The outbreak of World War II prevented this multi-centre trial being put into execution, but Fraser (1945) carried out in one centre, Glasgow, the trial which should have been conducted in many centres throughout Great Britain. Some 3 years ago Sir Stanley again observed that the only thing we really knew about gold therapy after 30 years of using it was that it produced several toxic effects. He suggested that the multi-centre "double-blind" controlled trial previously contemplated and planned should be put into execution by the Research Sub-Committee of the E.R.C. This was done; the present report gives the results of that trial.

Gold salts, employed widely in the treatment of tuberculous disease after World War I (Møllgaard and others, 1924), were first given by Landé (1927) to fourteen arthritic patients and by Pick (1927) to two, the former reporting benefit, the latter none. It was, however, the papers published by Forestier (1929, 1932, 1934), in which he claimed beneficial results in a large series of cases of rheumatoid arthritis, that brought chrysotherapy to the attention of the medical profession in many parts of the world, including Great Britain. As a result, many reports on therapeutic trials with gold were published, including papers by Slot and Deville (1934), Buckley (1934), Hartfall and Garland (1935, 1936), Pemberton (1935), Bach (1936), Hartfall, Garland, and Goldie (1937), Copeman and Tegner (1937), and others following soon after. These workers claimed that considerable benefit resulted but that the incidence of toxic side-effects was higher than that reported by Forestier; thus Hartfall and others (1937) recorded 40 per cent. of treated cases as suffering from toxic reactions. These included rashes, stomatitis, intestinal colic, diarrhoea, vomiting, icterus, purpura, and one case of agranulocytosis. Renal damage, varying from albuminuria to severe toxic nephritis, and hypoplasia or complete aplasia of the bone marrow were found to be additional serious complications which might occur. Hartfall and others (1937) also noted that gold salts were of doubtful value when used in forms of arthritis other than rheumatoid arthritis.

Although these extensive trials had been carefully carried out, the failure to include a control series of

* The following have served as Members of the Research Sub-Committee at some time during the period covered by this trial:

Ex Officio

Dr. W. S. C. Copeman (*Chairman of the Council*)
Dr. O. Savage (*Hon. Med. Secretary*)
Dr. R. M. Mason (*Deputy Hon. Med. Secretary*)
Dr. E. Lewis-Faning (*Hon. Med. Statistician*)
Prof. Sir Stanley Davidson

Ordinary Members

Dr. A. G. S. Hill (*Chairman*)
Prof. E. G. L. Bywaters
Mr. W. D. Coltart
Dr. J. J. R. Duthie
Prof. J. H. Kellgren
Dr. J. H. Glyn
Dr. L. E. Glynn
Prof. C. H. Gray
Dr. F. Dudley Hart
Dr. G. D. Kersley
Mr. G. Lloyd-Roberts
Prof. N. F. Maclagan
Prof. G. A. Smart
Dr. H. F. West

The report was prepared jointly by Dr. F. Dudley Hart (Chairman at the initiation of the trial) and Dr. E. Lewis-Faning (Hon. Med. Statistician to the Empire Rheumatism Council), with the assistance of all members of the Research Sub-Committee. The *x*-ray films were assessed by Dr. Ifor Pennant Williams.

patients treated with placebos given by injection makes it difficult to assess the value of the conclusions reached. Between 1940 and 1958, the results of trials incorporating a control series of patients not treated with gold, were reported by Ellman, Lawrence, and Thorold (1940), Fraser (1945), Waine, Baker, and Mettier (1947), Adams and Cecil (1950), and Lockie, Norcross, and Riordan (1958). Of these studies the only one which conformed to modern control requirements, *i.e.* a "double-blind" trial in which neither the patient nor the physician knows which subjects receive gold and which placebos, was the trial reported by Fraser (1945), which had been carried out as part of a multicentre investigation planned in 1939 by the E.R.C.

Ellman and others (1940) divided their patients into three groups of thirty. The first group received 0·2 g. Solganol B weekly, the second group received 0·1 g. weekly, and the control group received sterile almond oil, all administered by intramuscular injection. Treatment was continued for 9 months in each case, with a rest period of 6 weeks half way through the course. In all three groups there were several patients whose illness had lasted only a few months. The method of allocating cases is not recorded and the physicians knew to which group each patient belonged, *i.e.* it was not a "double-blind" trial. When a patient was free of joint pain, with painless movements and a normal erythrocyte sedimentation rate, the disease was considered inactive. At the end of the 9-month period of therapy the disease was considered to be inactive in fourteen (47 per cent.) of the first group, in eight (27 per cent.) of the second group, and in one (3 per cent.) of the control group. Toxic effects occurred more commonly in the first (large dose) group (eight stomatitis, eight dermatitis, one agranulocytosis, and one jaundice), as compared with one stomatitis and five dermatitis in the second (small dose) group. Of 25 complications, 24 occurred when the erythrocyte sedimentation rate had become normal.

Fraser (1945) reported 110 cases with active disease of 2 to 5 years' duration. Patients were observed for only one year. Of 57 patients given a total of 1·0 g. Myocrisin by weekly intramuscular injections of 0·1 g., 24 were found to be "greatly improved" and twelve "moderately improved", compared with four and six respectively in the control group of 46 patients. "Great improvement", as assessed by the physician, occurred, therefore, in 42 per cent. of the treated as compared with 8 per cent. of the controls, though the patients' own assessments of their condition gave a figure of 56 per cent. greatly improved in the treated group as compared with 33 per cent. in the control group. Of nineteen "incapacitated" patients, seventeen were able to resume employment in the treated group, as compared with four of fourteen in the control group. Treatment was stopped because of toxic reactions in four of the treated patients and three of the controls.

Waine and others (1947) studied 58 patients with active rheumatoid arthritis treated with gold. All received a total dose of at least 0·5 g. gold (as sodium aurothiomalate or aurothiosulphate), the average dose being 1·6 g. of the metal. Injections were given at weekly, bi-weekly, or monthly intervals. A series of 62 consecutive patients with rheumatoid arthritis treated only by "supportive" therapy was used as a control group. Since they received no injection of a placebo the trial cannot be considered satisfactory by modern standards. The authors state that the rate of significant improvement was twice as high in the gold-treated cases as in the controls (57 per cent. as compared with 29 per cent.).

Adams and Cecil (1950) reported a series of 106 patients with rheumatoid arthritis treated by chrysotherapy during the first year of their illness, and compared it with a series of 83 cases given conventional therapy without injections. There was thus no satisfactory control series. Two preparations of gold were used—Solganol B oleosum (aurothioglucose) and Myocrisin (sodium aurothiomalate). The initial dose was 10 mg., rising to 50 mg. in the majority of cases, although some received 100 mg. at weekly intervals. The total amount of gold in a course was 1·0-1·5 g. "Remission" occurred in 66 per cent. of gold-treated cases one year after the institution of therapy, but only in 24·1 per cent. of the control group. When a remission occurred it did so on an average some 10 months later in the control group than in the gold-treated group (17·1 months and 7·1 months respectively). The average time from remission to later relapse, when it occurred, was the same in both groups—27 months. Their conclusions were that chrysotherapy increases the incidence and accelerates the appearance of remissions if administered during the first year of the disease.

Lockie and others (1958) compared 507 patients who received gold salts with 566 "control" patients who had never had chrysotherapy. The control group received no injections of a placebo. No details are given of the comparability of the two groups as regards age or duration of disease. The majority of patients received sodium aurothiomalate, but a few were given aurothioglucose. The gold salt was administered intramuscularly at weekly intervals, beginning with a dose of 10 mg.,

then 20 mg., then 40 mg., until a total of 500 mg. had been given. Thereafter the dose was determined by the clinical condition of the patient. The authors state that a minimal amount of 300 mg. of the gold preparation was required before the course of the disease was favourably influenced. The authors concluded that the use of gold salts affords patients a 20 per cent. better chance of complete recovery or of major improvement.

In all the reports discussed above, the authors claimed that the patients treated with gold received some benefit and that when a control series was incorporated in the trial, the treated cases showed greater improvement than the controls. In contrast, two other reports claim no difference between the treated and the control groups. Thus, Merliss, Axelrod, Finebury, and Melnik (1951) compared a control series of 44 subjects with rheumatoid arthritis, who received saline or serum injections, with 27 subjects who received a slow-acting gold preparation, aurothioglycolanilide (Lauron). No case was treated for less than 6 months. Dosage, duration of therapy, and frequency of injections varied in different cases. The degree of subjective improvement and the fall in the erythrocyte sedimentation rate was stated to be similar in the treated and control series.

Brown and Currie (1953) gave injections of gold, copper, saline, and arsenic at weekly intervals to 38, 60, 60, and 21 patients with rheumatoid arthritis, physiotherapy to 22, and aspirin by mouth to 19. The total dose of gold was 0·8-1·0 g. sodium aurothiomalate, divided over thirteen injections. Assessed at the end of the course of injections and at 3 and 12 months later, chrysotherapy did not emerge, by any mode of assessment, as a superior form of therapy.

Assessment of the duration of beneficial results after the completion of treatment with gold has been made by two groups of workers. Snorrason (1952) compared 295 gold-treated cases with 169 patients who had never received chrysotherapy. The preparation used was Sanocrysin, given intravenously in doses of 25 to 100 cg. at 5- to 7-day intervals. The number of injections varied from two to seven, depending on the reactions and general condition of the patients. The author claimed that after 4 years 72 per cent. of the gold-treated patients were "arrested" as compared with 23 per cent. of the control series, but relapses set in subsequently, so that after 10 years both groups showed an equal return of progressive disease. Ragan (1951) studied the same problem and came to a similar conclusion, namely, that gold salts did not permanently alter the natural course of the disease.

The editors of the comprehensive Rheumatism Review in the *Annals of Internal Medicine* (1959) state: "The value of gold therapy continues to have solid support from those clinicians most experienced in its use, but statistical proof of its efficacy is still lacking."

In view of the criticisms made of most of the trials discussed above, and because of the conflicting results obtained in those trials which were best controlled, the E.R.C. felt that there was a real need for making a carefully controlled investigation into the value of gold in rheumatoid arthritis.

(2) General Design of the Trial

For this "double blindfold" trial, 200 patients with rheumatoid arthritis were divided equally into two groups, balanced for sex, age, and duration of disease.

Patients in the Treated Group (alternatively termed the "gold" group) were given a total of 1 g. sodium aurothiomalate over a period of 20 weeks by intramuscular injection of 50 mg. at weekly intervals.

Patients in the Control Group were given a total dose of 0·01 mg. (1/100 mg.) sodium aurothiomalate over 20 weeks by injection of 0·5 μg. at weekly intervals. The controls therefore received 1/100,000 the quantity of gold that the treated group received.

Both groups were given simple supportive measures—namely, rest, splints, aspirin, and physiotherapy. All injections were given in the participating units.

The trial was designed to permit comparison of the two groups as regards:

(1) Clinical and functional assessments at 1, 3, 6, 12, 18, and 30 months after treatment was started.

(2) Radiological change over 18 and 30 months.

(3) The number of patients who had to be withdrawn from the trial, or for whom a change of treatment became essential.

(4) The incidence of complications.

This report presents the results during the 18 months after the start of the trial, *i.e.* to approximately 1 year after each patient had completed the course of treatment.

(3) Criteria for Admission to the Trial

Patients were eligible for admission if they:

(*a*) Were attending for out-patient treatment.

(*b*) Had had active rheumatoid arthritis for not less than 1 year and not more than 5 years.

(*c*) Were aged 20 to 64 years.

(*d*) Had bilateral involvement of hands and/or wrists (*i.e.* one hand and opposite wrist, both hands, and/or both wrists) in addition to the involvement of at least one other joint.

(*e*) Had an erythrocyte sedimentation rate (Westergren) of 20 mm. or more in 1 hour.

(*f*) Had not previously received gold therapy.

(*g*) Had not received chloroquine, phenylbutazone,* or systemic steroid therapy (corticotrophin, cortisone, prednisone, or prednisolone) in the 3 months preceding admission to the trial.

(4) Allocation of Patients to Treatment

Gold was supplied† for the treated group in 1-ml. ampoules containing 50 mg. sodium aurothiomalate, and for the control group in 1-ml. ampoules identical in appearance containing 0·5 μg. sodium aurothiomalate.

Stocks of the ampoules were held centrally by the statistician.

24 centres participated in the trial (see Appendix II), but, because of the stringent criteria for admission to the trial, the selection of eight to ten patients at any one centre was not easy and in the event the assembling of 200 patients occupied 18 months—from January, 1957, to May, 1958. To ensure that males and females should be represented in the same proportions in the gold and control groups, each centre was asked to submit the names of "even" numbers of each sex (2 males and 6 females; 4 males and 4 females, etc.).

When a suitable patient presented, particulars of the name, sex, age, and duration of disease were sent to the statistician, who then allocated the patient to one of the two groups according to a pre-arranged randomized system—ensuring that in the aggregate the treated and the control groups would be balanced in regard to sex, age, and duration of disease. He then despatched sufficient supplies for the total course of injections, labelled only with the patient's name. This system ensured that neither the patient nor the assessor knew to which of the two groups the patient had been allocated. That this ignorance was maintained is supported by the fact that it had been agreed that after the 18th-month assessment a second course of injections could be given at the discretion of the physician in charge; slightly more requests for a second course were made on behalf of the controls.

A proforma for recording the assessments (Appendix I) accompanied the drug, as well as a post-card for notifying the statistician of the exact dates on which treatment was started and the initial *x*-ray film was taken.

Because of one late cancellation, the treated group comprised only 99 instead of 100 patients.

In the event (see Appendix II) it proved impossible for every centre to obtain even numbers of each sex but, in the aggregate, the treated and control groups as initially comprised were similar as regards the three factors (sex, age, and duration of disease). Males comprised 29 per cent. of each group. The mean age of all 99 patients in the gold group was 48·7 years, and that of the 100 controls was 48·6 years. The disease was of short duration (1-3 years) in 66 and 68 per cent. respectively, and of longer duration (3-5 years) in 33 and 32 per cent. respectively.

(5) Withdrawals and Changes of Treatment

The criteria were regulated by the following instructions:

(*a*) The course of injections was to be continued for the whole period of 20 weeks, whether a remission occurred or not.

(*b*) The course should be discontinued only for serious toxic effects. Milder side-effects should be met by a reduction of the weekly dose and corresponding extension of the treatment period to not more than 25 weeks.

(*c*) Each patient's medical practitioner should be informed that the patient was being put on a course of gold and that a controlled investigation was being carried out. He was asked not to prescribe any other form of therapy coincidentally and was specifically requested to withhold corticosteroids and phenylbutazone.

(*d*) If deterioration occurred to such an extent as to necessitate other treatment—in particular with corticosteroids or phenylbutazone—assessments should be continued but the new treatment should be noted on the record form. Admissions to hospital and the reason for such should also be recorded.

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* In order to speed up the selection of the last forty patients, the requirement that phenylbutazone should not have been previously received, was relaxed.

† Messrs. May and Baker Ltd.

(*e*) In emergencies, the physician in charge could be informed whether the patient was in the gold or the control group, and this was in fact done in three instances: because of dermatitis in one case, thrombocytopenic purpura in the second, and haematemesis attributed to thrombocytopenic purpura in the third. All these three patients were receiving gold salts.

(*f*) During the first 18 months of the trial, *i.e.* until one year after the end of completing the course of injections, no treatment other than as stated in Section 2, should be given.

(6) Assessment

Indices for comparing the progress of the two groups were derived from data recorded on the standard proforma (Appendix I) at each examination. For the initial assessment, two examinations were made on consecutive weeks: Week −1 and Week 0 (the latter being the date of the first injection).

Data recorded at the first assessment and at every subsequent examination comprised:

1. Functional capacity (physician's estimate) in five grades.
2. Subjective estimate of fitness by the patient in five grades.
3. Assessment of joints involved (42 joints were listed).
4. Strength of grip in each hand (mm. Hg).
5. Haemoglobin concentration (g. per cent.).
6. Erythrocyte sedimentation rate (mm./hr, Westergren).
7. W.B.C. (total and differential counts) per cu. mm.
8. Sheep cell agglutination test (S.C.A.T.) initially and at 18 and 30 months.
9. Complications present at, or occurring between, each assessment.
10. Number and nature of analgesic tablets taken daily (assessed retrospectively at each attendance).
11. Radiological examination of hands and wrists initially and at 18 and 30 months.

Details of the conventions laid down to secure uniformity of assessment are given in their respective sections.

(7) Withdrawals (Table I)

Strictly speaking, all patients who, for any reason, failed to complete the course of twenty weekly injections, or who could not be examined at the required 12- and 18-month points, or had to be given other forms of therapy, were withdrawals. These numbered 35, of whom 24 were on gold. As will appear later, it was not necessary to discard entirely the records of all of these patients from the analysis.

The reasons for withdrawal, in four broad groups, are shown in Table I.

Toxicity.—Toxic reactions in the *gold* group, involving fourteen withdrawals, included ten cases of dermatitis, four of which were severe enough to need admission to hospital.

One of these patients died from pneumonia complicating bronchitis in the fifteenth month. He was a 58-year-old male with rheumatoid disease of one year's duration, who developed a slight generalized pruritus in the third month. Gold therapy was discontinued after eleven injections, but the rash persisted and he was admitted to hospital for treatment of it 4 months later. Seven months later, that is, 11 months after discontinuing gold therapy, he developed pneumonia on pre-existing chronic bronchitis and died. Gold therapy undoubtedly caused his dermatitis, but in the opinion of his physician it was in no way responsible for his death.

TABLE I

REASONS FOR WITHDRAWAL IN THE TWO GROUPS

Group		Gold	Control
Toxicity (mainly rash)	Less than ten injections	3	2
	Ten to twenty injections	11*	2*
Deterioration needing Change of Treatment	Put on steroids at 9 months (gold)	1	—
	Put on steroids at 3 months (control)	—	1
	Changed at 14 to 16 months	2*	2*
Death at 13th Month: Carcinoma of Uterus		1*	0
Failure to Attend		6 (1*)	4 (2*)
Total		24	11

* Included in the analysis at least to the 12th month (see text p. 100).

Of the other three patients with gold dermatitis of sufficient severity to warrant admission to hospital, one male aged 57 was detained for 17 days with a generalized eruption, which developed in the third month of treatment; one female aged 48 developed a rash in the eighth week, which cleared on dimercaprol after a 15-day stay in hospital; and one male aged 40 developed a gold dermatitis after thirteen injections. The erythrocyte sedimentation rates of these three cases at the time of the development of the rash were 50, 8, and 56.

Even in these "severe" cases the patient's condition was never critical, and in seventeen less severe cases of dermatitis the systemic effects were of minor importance.

The remaining four withdrawals because of toxic reactions were due respectively to oedema and malaise in the first month; stomatitis in the third month; corneal ulcer in the third month; and thrombocytopenic purpura, hepatitis, and pulmonary embolism just after the twelfth month.

All but three of the fourteen withdrawals received more than half of the total injections and are included in either the 18-month assessment (ten cases) or the 12-month assessment (eleven cases). The case of purpura and hepatitis noted above suffered a severe relapse of his rheumatoid arthritis, was admitted to hospital for a period of 5 months, and was finally withdrawn from the trial and given steroid therapy.

In the *control* group, two out of four cases of "toxicity" are included in the analysis: one with stomatitis and the other with a rash treated at 12 months with chloroquin and at 15 months with corticotrophin. The other two patients, who developed rashes and/or albuminuria, are excluded since they received only five injections.

Deterioration.—Of the three cases deteriorating on gold, one was given steroids at the ninth month and is excluded, while the other two were given phenylbutazone at the fourteenth month and triamcinolone at the sixteenth month respectively and are included.

In the *control* group, one case given steroids after ten injections is excluded, and two given steroids at 14 and 16 months respectively are included.

In brief, the withdrawals comprise two groups:

Patients	Gold-Treated	Controls
Group 1 (Complete withdrawals)	9	5
Group 2 (Partial withdrawals)	15	6
Total	24	11

Only those in Group 1 (the fourteen complete withdrawals) were entirely excluded from the analysis. Their exclusion reduced the number in the trial to 90 treated patients and 95 controls.

The statistical analysis which follows was carried out both including and excluding the withdrawals in Group 2. Every tabulation was done both ways—but for reasons of space only those in which these 21 withdrawals were included are published here. In no instance did the results differ materially when Group 2 withdrawals were excluded.

(8) Complications

Table II shows the incidence of complications in each group. These occurred in 21 patients in the gold group and twelve in the control group; if the cases withdrawn from the series are added, the figures are 35 : 16. A few patients had more than one complication. Most of these side-effects were skin reactions, 22 in the gold group and seven in the controls, all the latter being relatively mild.

TABLE II

COMPLICATIONS RECORDED IN THE TWO GROUPS

Group		Gold	Control
No. of Patients with Complications	(*a*) Not necessitating withdrawal	21	12
	(*b*) Necessitating withdrawal (see Table I—"Toxicity") ..	14	4
	Total	35	16
Complications	Dermatitis (severe)	4	0
	Dermatitis (less severe)	17	7
	Pneumonia, rash, death	1	0
	Purpura (hepatitis in one)	2	1
	Albuminuria	4	3
	Stomatitis or gingivitis	3	2
	Oedema and malaise	1	3
	Corneal ulcer or keratitis	2	0
	Fever	1	0
	Flare of arthritis	1	1
	Ulcer or haematemesis	2	0
	Dyspepsia	3	0

Apart from these skin reactions, toxic effects were infrequent in either group, though there were four cases of albuminuria in the gold group as compared with three in the control group. In the four patients on gold the albuminuria disappeared spontaneously within a month of its appearance; in one patient it appeared with two separate courses of gold, after the seventeenth injection in the first course, and after the fourteenth in the second. Renal function tests were normal.

In this study, therefore, complications were noted in about one-fifth of the gold-treated cases and one-eighth of the control series; if withdrawals are added, 35 per cent. of the gold-treated cases as compared with 16 per cent. of the controls suffered toxic side-effects. The only troublesome side-effects were present in the gold-treated cases. It is clear that such side-effects were significantly more frequent in the gold group, but they were seldom serious or severe.

(9) Comparison of Gold and Control Groups at Beginning of Trial (Tables III and IV)

Table III and Table IV (overleaf) show that the two groups were similar at the start of the trial in respect of all the factors examined. In the detailed analyses these tabulations were made in three sections (A, B, and C) in which the comparison between the treatment and control groups was based respectively on:

(A) All entrants (Gold 99, Controls 100).

(B) All entrants less Group 1 (complete) withdrawals (Gold 90, Controls 95)—see Section 7.

(C) Excluding both Group 1 and Group 2 withdrawals (Gold 75, Controls 89)—see Section 7.

The differences referred to throughout the report are considered to be statistically significant only if they attain the 0·05 probability level. (Any exceptions to this rule are specifically stated.) No

TABLE III

SIMILARITY OF THE GOLD-TREATED AND CONTROL GROUPS AT START OF TRIAL AFTER EXCLUDING GROUP 1 WITHDRAWALS‡

Factors Compared		Group	
		Gold	Control
No. of Patients		90	95
No of Males		26 (29%)	27 (28%)
Mean Age (yrs)		48·7±0·98	48·6±0·98
Duration of Symptoms (yrs)	1 to 3 3 to 5	59 (66%) 31 (34%)	65 (68%) 30 (32%)
Type of Onset	Acute Non-acute Not known	29 (32%) 59 2	25 (26%) 70 —
Mean Number of Joints Involved	Total	17·3±0·92	19·2±0·95
	Girdle Intermediate Peripheral	0·9 1·5 14·8	0·8 1·6 16·8
Functional Capacity ("Mean")* (Physician's Assessment)		2·3	2·2
Fitness (Mean)—"Estimated by Patient" (per cent.)		59·5	60·2
Mean Strength of Grip	Right Left	144·5 148·9	144·8 144·8
Mean Haemoglobin Concentration (g. per cent.)		12·4±0·17	12·3±0·15
Mean Erythrocyte Sedimentation Rate (mm./hr, Westergren)		41·6±2·07	37·9±1·96
S.C.A.T.†	Negative −5 to −3 Negative −2 to −1	2 19	7 13
	Positive 0 to +1 Positive +2 to +3 Positive +4 to +7	20 22 15	25 22 16
	Not known	12	12

* The use of the term "Mean" here and in Tables IV and V is unjustifiable statistically, but convenient as an index to summarize the distributions.

† Minimal positive titre at each centre = 0 (see also Results—S.C.A.T.).

‡ See Section 7.

TABLE IV

SIMILARITY OF THE TWO GROUPS AT START OF TRIAL

(GOLD 90; CONTROLS 95.—INITIAL FUNCTIONAL CAPACITY)

(*i*) Functional Capacity (Physician's estimate),† showing percentage in each grade

Group	Grade					Mean Grade*
	1 (best)	2	3	4	5	
Gold	9	53	34	3	—	2·3
Control	12	57	32	—	—	2·2

(*ii*) Functional Capacity (Patient's own estimate of fitness), showing percentage in each grade

Group	Grade (per cent. fit)					Mean Grade
	100	75	50	25	1	
Gold	3	42	44	10	—	59·5
Control	5	40	46	8	—	60·2

* See footnote to Table III.

† For definition of grades, see Section 11.

such differences could be demonstrated from the data in Tables III and IV.

Note on Grip Values

Because three types of sphygmomanometer—on which the possible *maximum* readings varied from 250 to 450—were distributed between the centres, the index "mean grip value" (Table III) is of doubtful validity. But when the distributions of grip value in broad categories in the two groups were compared and tested by χ^2 (all values of 250 and over forming a single category) again no real difference was apparent.

(10) Effect of Withdrawals on the Composition of the Groups

After a series of statistical tests it was not possible to deduce that the omission of Group 1 withdrawals alone, or Groups 1 and 2 withdrawals together, prejudiced the comparison of the two groups. The initial similarity of the groups when based on all the 199 entrants (A) still held good when Group 1 withdrawals were omitted (B), and also when both groups of withdrawals were omitted (C). Indeed, the values of each index were throughout so similar for A, B, and C that only the results of B are actually presented.

(11) Results

Comparison of Progress in the Two Treatment Groups

Functional Capacity (Table V)

(*i*) *Physician's Assessment.*—This was estimated objectively on the basis of examination and interrogation in five grades:

(1) Fully employed or employable in normal work and able to undertake normal physical recreations.

(2) Fully employed in special work after vocational training, or doing light or part-time work in normal occupation. Limitation in the amount of physical recreation that could be taken. Housewives able to do all but the heaviest housework.

(3) Not employed or unemployable. Very limited physical activity and little or no capacity for physical recreation. Housewives able to do light housework and/or limited shopping only. In-patients in hospital for treatment but up and about in the ward.

(4) Confined to hospital, house, or wheel-chair, but able to look after themselves in the essentials of life. In-patients in hospital for treatment sitting up but not getting about.

(5) Confined to bed and unable to look after themselves. In-patients on complete rest in bed.

Table V (opposite) shows the percentage with given grades of severity at each assessment in each group. The "mean"* grades (last column) indicate that both groups improved in function during the trial—the gold group perhaps more than the controls—a possibility now to be examined further.

At the start, about 10 per cent. of both groups were in Grade 1, *i.e.* the highest functional grade. Little change was apparent during the first month, but after 3 months, 22 per cent. of the gold group as against only 15 per cent. of the controls were in this top grade. By the end of the injection period

* Adopted as a convenient summarization of the distributions although statistically unjustifiable because the grades are not quantitative but qualitative.

TABLE V

FUNCTIONAL CAPACITY (PHYSICIAN'S ESTIMATE) AT PERIODICAL ASSESSMENTS
(GOLD 90; CONTROLS 95)
PERCENTAGE IN EACH GRADE AT EACH ASSESSMENT

Month of Assessment	Group	Grade					"Mean" Grade*
		1 = best	2	3	4	5	
0	Gold	9	53	34	3	—	2·3
	Control	12	57	32	—	—	2·2
1	Gold	9	62	26	3	—	2·2
	Control	14	54	33	—	—	2·2
3	Gold	22	57	20	1	—	2·0
	Control	15	64	20	1	—	2·1
6	Gold	41	47	11	1	—	1·7
	Control S	23	60	16	1	—	2·0
12	Gold	40	44	12	1	2	1·8
	Control S	23	55	22	—	—	2·0
18	Gold	43	42	13	2	—	1·7
	Control S	25	49	25	—	—	2·0

* See footnote to Table III.
S = Significant difference between the distribution of the two groups.

this advantage was increased, the proportions in Grade 1 being 41 per cent. of the gold group as compared with 23 per cent. of the controls, and the distributions were significantly different ($\chi^2 = 6{\cdot}2$, $P < {\cdot}05$). At the 12th month the position was the same, and at the 18th month there were 43 per cent. of the gold group in Grade 1 as compared with only 25 per cent. of the controls.

An almost identical picture was produced when Group 2 withdrawals (see Section 7) were omitted.

Re-grading.—Table VI shows that a larger percentage of patients on gold than controls were upgraded at every assessment. At the 12th and 18th month more controls were downgraded than upgraded, but this was true of the gold group only at the 12th month.

Comparing the 18th month with the initial assessments (last line of Table), 26 per cent. of the controls, but 56 per cent. on gold—more than double the proportion—finished in a better grade than they started. 9 per cent. of both groups finished in a lower grade, and 65 per cent. of the controls but only 35 per cent. on gold finished in the same grade.

The last two columns of Table VI take into account

TABLE VI

RE-GRADING OF FUNCTIONAL CAPACITY (PHYSICIAN'S ESTIMATE), SHOWING PERCENTAGE OF TOTAL RE-GRADED AT EACH ASSESSMENT
(GOLD 90; CONTROLS 95)

Month of Assessment	Group	Upgrading	Downgrading	No Change	Actual as Percentage of Possible Scores	
					Upgrading	Downgrading
1	Gold	12	3	84	9	1
	Control	4	3	93	4	1
3	Gold	24	1	74	20	0·4
	Control	14	2	84	12	0·7
6	Gold	28	1	71	29	0·4
	Control	15	1	84	14	0·7
12	Gold	11	15	74	15	6
	Control	6	12	82	8	4
18	Gold	9	6	84	13	2
	Control	6	9	85	7	3
Complete 18 months	Gold	56 S	9	35	51 S	4
	Control	26	9	65	25	4

S = Significant difference.

the *amount* of upgrading and downgrading which was *possible* for each group of patients—*i.e.* the amount of change which actually occurred is expressed as a percentage of that which was possible. To illustrate the method, consider the initial grading of the ninety patients on gold: eight were in Grade 1 and could not therefore be upgraded at all; 48 were in Grade 2 and could each have moved up one grade (48); 31 were in Grade 3 and could each have moved up two grades (62); three were in Grade 4 and could each have moved up three grades (9). Thus the total possible score for upgrading in the first month (or for the whole period) in the gold group was 48 + 62 + 9 = 119. The actual score at the end of the first month was 11, *i.e.* 9 per cent. of the possible score. Over the whole 18 months the actual score was 51 per cent. of the possible score; for the controls it was only 25 per cent.

The figures were not affected when the Group 2 withdrawals were omitted, the actual figures as a percentage of the possible scores for the whole period still being gold 51 per cent. and controls 25 per cent.

(*ii*) *Patient's Own Estimate of Fitness* (Table VII).—For the subjective estimate of function, the patient graded his own condition at each assessment as 100, 75, 50, 25, or 1 per cent. fit. The analysis of these results supports the objective assessments of the previous section. The mean grade rose in both groups during the period of injections and with advantage to the gold group. During the follow-up period there was some slight retrogression.

At the end of the injection period of 6 months, the percentage of patients describing themselves as 100 per cent. fit were 41 and 22 per cent. for the gold and control groups respectively, compared with 3 and 5 per cent. at the start of the trial. At the eighteenth month, 37 per cent. of the treated group and 23 per cent. of the controls described themselves as completely fit.

The omission of the withdrawals did not affect these results.

Re-grading.—Table VIII (opposite) shows that the percentage of patients who felt improved (upgraded) at each successive assessment after 1, 3, and 6 months was substantial in both groups, but after the injections ended the proportions upgraded were smaller and similar in both groups.

Expressing the actual score as a percentage of the possible score for upgrading, significant differences between the two groups occur at the third and sixth months, and over the 18 months as a whole.

63 per cent. of the gold group, but only 48 per cent. of the controls, assessed themselves as more fit at the end of the trial than at the start (last line of Table). The actual/possible score during the 18 months was 50 per cent. for the gold group and 38 per cent. for the controls.

Similar results were obtained when the withdrawals were omitted.

Joints Involved, Clinical Assessment

A joint was considered affected if two out of three features—swelling, tenderness, limitation of movement—were present. The 42 joints examined at each clinical assessment comprised proximal interphalangeal and metacarpophalangeal joints (20),

TABLE VII

SUBJECTIVE WELL-BEING (PATIENT'S OWN ESTIMATE), SHOWING PERCENTAGE IN EACH GRADE AT EACH ASSESSMENT
(GOLD 90; CONTROLS 95)

Month of Assessment	Group	Functional Capacity (per cent. "fit")					Mean Grade
		100	75	50	25	1	
0	Gold	3	42	44	10	—	59·5
	Control	5	40	46	8	—	60·2
1	Gold	8	40	41	9	2	60·2
	Control	5	44	42	8	—	61·2
3	Gold	20	51	26	3	—	70·6
	Control	11	54	33	2	1	67·0
6	Gold	41	46	12	1	—	78·8
	Control S	22	53	22	2	1	71·7
12	Gold	35	47	11	4	2	74·7
	Control S	18	56	24	2	—	71·1
18	Gold	37	41	19	2	1	75·1
	Control S	23	47	27	2	—	71·2

S = Significant difference between the distributions of the two groups.

TABLE VIII

RE-GRADING OF FUNCTIONAL CAPACITY (PATIENT'S OWN ESTIMATE), SHOWING PERCENTAGE OF TOTAL RE-GRADED AT EACH ASSESSMENT
(GOLD 90; CONTROLS 95)

Month of Assessment	Group	Upgrading	Downgrading	No Change	Actual as Percentage of Possible Scores	
					Upgrading	Downgrading
1	Gold	17	11	72	10	6
	Control	12	7	81	7	3
3	Gold	43	1	56	30 S	0·5
	Control	29	5	65	19	2
6	Gold	38	2	60	37 S	0·8
	Control	25	3	72	20	1
12	Gold	10	20	70	14	9
	Control	13	17	71	13	6
18	Gold	14	12	73	16	4
	Control	13	12	75	12	5
Complete 18 months	Gold S	63	6	31	50 S	3
	Control	48	10	42	38	4

S = Significant difference between the two groups.

metatarsophalangeal (10), wrists, elbows, shoulders, hips, knees, and ankles (12).

At the start of the trial the mean number of joints affected per patient was not significantly different in the two groups—17·3 per patient in the gold group and 19·2 per patient in the control group (Table IX). At the assessment after 18 months the mean for the gold group had been reduced by more than one half (to 8·0 joints), but that for the control group by only one third (to 12·5). The differences between the means of the two groups were significant at the 3rd month and at subsequent assessments.

The 42 joints were also considered in three groups:

(1) Peripheral—hands, wrists, feet, and ankles (34).
(2) Girdle—shoulders and hips (4).
(3) Intermediate—elbows and knees (4).

The mean number of peripheral and intermediate joints affected became significantly less in the gold group from the third month onwards; for the girdle joints the trends followed the same pattern but the differences did not reach significance level.

Newly Affected, Quiescent, and Re-activating Joints.—At each assessment, the number of active joints for any patient, and therefore the mean for a group of patients can also be calculated by adding to the number of joints active at the previous assessment, the number of newly affected and the number of re-activating joints, and deducting the number becoming quiescent.

The following conventional definitions were adopted:

A *newly affected* joint is one recorded as active for the first time during the survey period.
A joint becoming *quiescent* is one recorded as active at the previous but not at the current assessment.
A *re-activating* joint is one which was recorded at any previous assessment (during the trial) as becoming quiescent, but which at the current assessment was again active.
(There could be no re-activating joints at Month 1 because there was no earlier assessment at which they could be recorded as quiescent.)

These definitions of necessity ignore any compensatory changes occurring between assessments—

TABLE IX

MEAN NUMBER OF JOINTS INVOLVED PER PATIENT AT EACH ASSESSMENT
(GOLD 90; CONTROLS 95)

Group	Month of Assessment					
	0	1	3	6	12	18
	Mean ± S.E.	Mean ± S.E.	Mean ± S.E.	Mean ± S.E.	Mean ± S.E.	Mean ± S.E.
Gold	17·3 ± ·92	14·3 ± ·86	10·5 ± ·73 S	7·8 ± ·67 S	7·5 ± ·76 S	8·0 ± ·81 S
Control	19·2 ± ·95	15·6 ± ·79	14·0 ± ·87	12·6 ± ·95	12·7 ± ·91	12·5 ± ·95

S = Significant difference between the two groups.

such as a joint recorded active at both the sixth and twelfth months which may have become quiescent and re-activated again in the interim.

Table X shows the sequence of events and is to be read as follows:

The mean number of joints affected per patient in the gold group at the start of the trial was 17·3. After one month, the mean number of newly affected joints recorded per patient was 2·0, whilst the mean number recorded as quiescent was 5·0 (17·3 + 2·0− 5·0 = 14·3, the mean number active at month 1). Similar calculations have been made for subsequent assessments.

At every assessment after the first month, the mean numbers of newly affected and reactivating joints were higher in the control group. The mean number of quiescent joints was less in the control group at 3 and 6 months.

The resulting trend in the average number of joints affected per patient is best appreciated by expressing the successive values as percentages of the initial value (last line of Table). In the gold group there was a steady decline from 100 per cent. (Month 0) to 43 per cent. (Month 12) and then a slight increase at Month 18 to 46 per cent. The greatest decline was between the 3rd and 6th month —the latter half of the period of injections. The

TABLE X

MEAN NUMBER OF NEWLY AFFECTED, QUIESCENT, AND REACTIVATING JOINTS PER PATIENT AT EACH ASSESSMENT

(GOLD 90; CONTROLS 95)

State of Joints		Month of Assessment											
		0		1		3		6		12		18	
		Gold	Control	Gold	Control	Gold	Control	Gold	Control	Gold	Control	Gold	Control
Newly Affected		—	—	2·0	1·5	0·9	1·1	0·5	0·8	0·9	1·3	0·7	0·8
Quiescent		—	—	5·0	5·1	5·8	3·9	4·4	3·9	3·1	3·5	2·4	2·9
Reactivating		—	—	—	—	1·1	1·2	1·2	1·7	1·9	2·3	2·2	2·4
*Joints Involved	Mean No. per Patient	17·3	19·2	14·3	15·6	10·5	14·0	7·8	12·6	7·5	12·7	8·0	12·5
	Percentage of Initial Number	100	100	83	81	61	75	44	66	43	66	46	65

* The mean values for "joints affected" which were computed independently for Table IX, can also be computed in this Table by successively adding to the value for any specific month, the mean of the newly affected and reactivating joints and deducting the quiescent joints: *e.g.* 14·3 (Month 1) + 0·9 + 1·1 − 5·8 = 10·5 at Month 3.

TABLE XI

NEWLY AFFECTED, QUIESCENT AND REACTIVATING JOINTS

(GOLD 90; CONTROLS 95)

ACTUAL AS PERCENTAGE OF POSSIBLE NUMBER

Joints Involved	Group	Month of Assessment					Total
		1	3	6	12	18	
Newly Affected	Gold	8·2 (2,224) S	3·9 (2,041) S	2·2 (1,962) S	4·1 (1,919) S	3·2 (1,764)	20·8 (2,113) S
	Control	6·4 (2,162)	5·2 (2,023)	4·2 (1,917)	6·6 (1,837)	4·4 (1,672)	24·8 (2,093)
Quiescent	Gold	28·2 (1,556)	39·6 (1,288) S	40·8 (947) S	39·7 (706) S	30·4 (672) S	
	Control	26·4 (1,828)	25·1 (1,483)	28·1 (1,329)	27·4 (1,198)	22·0 (1,204)	
Reactivating	Gold		23·0 (439)	12·9 (859) S	15·0 (1,143) S	15·4 (1,255) S	
	Control		23·2 (482)	22·4 (742)	22·7 (953)	20·8 (1,068)	
Became Quiescent and did not again Reactivate by 18th month	Gold	17·1 (1,556) S	24·1 (1,288) S	26·7 (947) S	27·9 (706) S		
	Control	12·6 (1,828)	11·1 (1,483)	16·0 (1,329)	18·9 (1,198)		

S = Significant difference between the two groups.

Figures in brackets indicate the "possible" numbers of joints on which the percentages are based. Thus, the possible number of:

Newly affected = Those not affected initially, less those which had become newly affected at earlier assessments.

Quiescent = Those active at the previous assessment.

Reactivating = Those which had become quiescent at earlier assessments.

decline in the controls was only to 66 per cent. (at Month 6) of the initial value and this level persisted until the end of the trial period.

Newly Affected Joints (Table XI).—A more refined index is obtained by expressing the actual number of newly affected joints as a percentage of the possible number—the possible number *at any assessment* being the summation (for all patients in the group) of the number of joints NOT initially affected, less the total which had become newly affected at earlier assessments.

Over the whole 18-month period (last column of Table) in the gold group 20·8 per cent. of joints not initially affected became active (440 out of a possible 2,113). In the control group 24·8 per cent. did so (519 out of a possible 2,093).

The difference between the groups varied at each assessment. At the end of the first month the index was 28 per cent. *higher* in the gold group than in the controls, but it was 25 per cent. lower at the third month. The gold group showed most advantage as regards newly involved joints at the sixth month—the end of the injection period—when the index was at a level only 52 per cent. of the control group.

After the first month the differences between the two groups were significant at every assessment except the last.

The figures for the three types of joints (Peripheral, Girdle and Intermediate) showed only slight deviations from the overall trend. For all three types, there was an excess of newly involved joints in the gold group at the end of the first month and this tendency was reversed in the third month; the main advantage to the gold group was at the 12th month for peripheral joints, and at the 18th month for girdle joints, but at the sixth month for the intermediate joints. The non-significant difference in the overall figures at the eighteenth month can be attributed to an excess of newly affected intermediate joints in the gold group at that assessment.

Joints which became Quiescent (Table XI).—Joints which were recorded as inactive at any specified assessment, but which were active at the preceding assessment, have been counted as becoming quiescent. Some became quiescent more than once during the trial. The average number per patient in the two treatment groups was shown in Table X.

To make allowance for possible differences in the number of joints which *could* become quiescent, the actual numbers were expressed as percentages of the possible numbers, *i.e.* the numbers active at the previous examination (Table XI).

The outstanding feature is the remarkable increase in this index at the third month when 39·6 per cent. of the possible number in the gold group compared with only 25·1 per cent. in the control group became quiescent. Furthermore, these levels were maintained at the sixth and twelfth months, but at the eighteenth month—one year after completion of therapy—a smaller percentage of the possible number became quiescent, particularly in the gold group (30·4 per cent.).

Similar trends and differences were apparent for each group of joints—peripheral, girdle, and intermediate—but for the last two types fewer significant differences could be demonstrated, probably because of the smaller number of joints involved.

Re-activating Joints (Table XI).—These comprise all joints which, having once been recorded during the trial as active, became quiescent and subsequently again active. Some joints became reactive more than once during the 18 months.

The average number per patient recorded as reactivating at each assessment was shown in Table X, but to allow for differences in the number of joints which *could* reactivate, the actual numbers were expressed as percentages of the possible numbers—*i.e.* the number of joints which were quiescent (as earlier defined) at the preceding assessment (Table XI).

At the end of the first month no joint *could* be recorded as reactivating. At the third month the percentage which did so was similar in each group (23 per cent. of those recorded as quiescent at the first month). But at the sixth month, only 12·9 per cent. in the gold group compared with 22·4 per cent. in the control group became reactivated, and this significant difference was materially unchanged at the twelfth and eighteenth months.

Peripheral joints showed a similar picture, but girdle joints showed no advantage to the gold group. Intermediate joints gave a statistically significant advantage at the sixth month, no difference at all at the twelfth month, and a non-significant advantage at the eighteenth month.

Quiescent Joints which did not Reactivate (Table XI).—The two groups have already been compared as regards the joints which became quiescent and those which again became active. In the final section of Table XI they are compared as regards the percentage of joints which became *and remained* quiescent, at least as far as the eighteenth month.

Although there was a small but significant advantage to the gold group in this respect even as early as the first month of therapy, the outstanding feature is the much higher proportion of joints in the

gold group which became inactive at the third, sixth, and twelfth months, and had not become active again by the eighteenth month (gold group 24 to 28 per cent. of the possible number, compared with 11 to 19 per cent. in the control group). Peripheral, girdle, and intermediate joints showed similar features.

Summary of Joints Affected.—The analysis of joints affected showed an advantage to the gold as compared with the control group, in that fewer joints became newly affected or reactivated, whilst more became quiescent and more stayed quiescent. These features were exhibited as early as the third month of the trial, and the number of active joints at the eighteenth month was reduced to 46 per cent. of the initial number in the gold group but to only 65 per cent. in the control group.

Throughout this section, the figures (of Tables IX to XI) were almost unchanged when the Group 2 withdrawals were omitted.

Strength of Grip (Table XII)

The strength of the grip of each hand was measured at each assessment in mm. Hg, with an initial bag pressure of 30 mm. maintained for 3 sec., the hand being held away from the body. The mean of two grips with each hand was recorded.

Special standard grip meters were supplied to each centre but (as noted in Section 9) three types of sphygmomanometer were used on which the maximum grip which could be recorded varied considerably. In the analysis, therefore, 250 mm. Hg was perforce taken as the maximum, although values above this (even up to 440) were actually recorded. As a result, the mean grip values in Table XII are minimal, but on the assumption that the three types of sphygmomanometer were similarly distributed between the gold and control groups, the means may be compared.

The Table shows that for each hand, the mean values (which were very similar for the gold and control groups up to the end of the first month of therapy) started to diverge at the third month, the gold group then showing a greater, but not a significantly greater, improvement. At the sixth and later assessments this difference became more pronounced, being outside the likelihood of a chance result. The mean grips of the two hands were very similar throughout, and when the withdrawal groups were omitted, they were materially unaltered.

From more detailed analysis (not shown in the Table) it was noted that the percentage of patients in the highest group (225+) increased over the 18 months in the gold group from 12 to 34 per cent. for the right hand and from 17 to 33 per cent. for the left hand, whereas the increases in the control group were only from 15 to 23 per cent. and from 13 to 22 per cent. for the right and left hands respectively.

Haemoglobin Concentration (Table XIII)

Both groups had approximately the same average concentration at the start of the trial (12·4 and 12·3 g. per cent. respectively). By the end of the course

TABLE XII

MEAN STRENGTH OF GRIP (mm. Hg)
(GOLD 90; CONTROLS 95)

Hand	Group	Month of Assessment					
		0	1	3	6	12	18
Right	Gold	144 ± 6	151 ± 6	167 ± 7	184 ± 6 S	177 ± 7	180 ± 7 S
	Control	145 ± 6	151 ± 7	155 ± 6	159 ± 6	162 ± 6	159 ± 7
Left	Gold	149 ± 6	147 ± 6	172 ± 6	183 ± 6 S	181 ± 6 S	180 ± 6 S
	Control	145 ± 6	147 ± 6	155 ± 6	157 ± 6	155 ± 7	155 ± 7

S = Significant difference between the two groups.

TABLE XIII

MEAN HAEMOGLOBIN CONCENTRATION (g. per cent. ± S.E.)
(GOLD 90; CONTROLS 95)

Group	Month of Assessment					
	0	1	3	6	12	18
Gold	12·4 ± 0·17	12·3 ± 0·14	12·5 ± 0·15	13·0 ± 0·13 S	13·1 ± 0·21 S	13·0 ± 0·11 S
Control	12·3 ± 0·15	12·4 ± 0·14	12·5 ± 0·14	12·6 ± 0·11	12·6 ± 0·19	12·4 ± 0·20

S = Significant difference between the two groups.

of injections these averages had been increased to 13 g. per cent. in the gold group and to 12·6 g. per cent. in the controls—a significant difference. By the end of the trial the control group level had fallen to 12·4 g. per cent., significantly lower than that in the gold group which remained at 13 g. per cent.

The same deductions could be drawn when the withdrawals were omitted.

Erythrocyte Sedimentation Rate (Table XIV)

At the beginning of the trial the mean erythrocyte sedimentation rate was slightly but not significantly higher in the gold group (42 as against 38 mm./hr). In both groups the level remained practically unchanged one month after the start of the trial, and at the third and sixth months it fell considerably in the gold group (to 21 mm./hr), but only slightly in the control group (to 33 mm./hr). At the eighteenth month it increased a little in the gold group (to 27 mm./hr); so that, whereas the third, sixth, and twelfth months showed real differences between the groups, at the eighteenth month the differences failed to reach significance (Table XIV). When the withdrawals were omitted, the results were barely altered.

White Cell Count (Table XV)

This investigation was not done consistently for every patient at each assessment, particularly as regards the differential count. The following comments were derived from the "total" counts of about 84 patients in the gold group, and 87 in the control group, and from polymorph counts in 66 and 70 patients respectively—not always the same patients at each assessment (Table XV).

The mean total W.B.C. in the gold group fell during the period of injections from an initial 8,200 to 7,000; rose at the twelfth month to 7,600, and fell again at the eighteenth month to 7,300. In the control group it fluctuated between 7,800 and 8,000 during the first 12 months but fell to 7,250 at the eighteenth month (Table XV).

Polymorphs varied between only 66 and 68 per cent. of the total count in both groups throughout the trial.

The evidence suggests that during the administration of gold the number of white cells was slightly reduced, and that this was equally true of polymorphs and lymphocytes.

It may be of interest to quote the number of patients in each group showing a total W.B.C. count

TABLE XIV

MEAN ERYTHROCYTE SEDIMENTATION RATE (mm./hr, Westergren)
(GOLD 90; CONTROLS 95)

Group	Month of Assessment					
	0	1	3	6	12	18
Gold	42 ± 2	43 ± 2	28 ± 2 S	21 ± 2 S	23 ± 2 S	27 ± 2
Control	38 ± 2	37 ± 2	36 ± 3	33 ± 2	34 ± 2	32 ± 2

S = Significant difference between the two groups.

TABLE XV

MEAN WHITE CELL COUNTS—TOTAL AND POLYMORPHS

White Cell Count	Group	Month of Assessment					
		0	1	3	6	12	18
Total	Gold	8,219 ± 409 (90)	7,352 ± 238 (82)	7,020 ± 243 (85) S	7,006 ± 195 (81) S	7,575 ± 274 (80)	7,292 ± 241 (84)
	Control	7,812 ± 202 (95)	8,099 ± 280 (89)	7,818 ± 266 (88)	7,764 ± 234 (87)	7,767 ± 239 (90)	7,247 ± 227 (91)
Polymorphs (per cent.)	Gold	67 ± 1 (77)	67 ± 1 (66)	67 ± 1 (68)	66 ± 1 (66)	68 ± 1 (65)	66 ± 1 (68)
	Control	67 ± 1 (81)	65 ± 1 (75)	66 ± 1 (70)	68 ± 1 (69)	66 ± 1 (72)	66 ± 1 (76)

Figures in brackets indicate the numbers of patients for whom W.B.C. readings were recorded, and on which the mean values are based.

S = Significant difference between the two groups.

below 5,000 in comparison with the number tested on each occasion:

Group	Month					
	0	1	3	6	12	18
Gold	3 (90)	7 (82)	13 (85)	10 (81)	8 (80)	9 (84)
Controls	2 (95)	4 (89)	5 (88)	6 (87)	5 (90)	8 (91)

Sheep-Cell Agglutination Test (S.C.A.T.)

This test is not standardized, and there were differences in technique at the various participating centres. As a result, what Centre X would record as 1/16, Centre Y might record as 1/32, and Centre Z as 1/128, etc. In order to aggregate the records of all Centres, the titre which each Centre regarded as the *minimal positive* was taken as 0, successive doubling dilutions above this as +1, +2, +3, etc., and titres below the minimum positive were recorded as −1, −2, −3, etc.

A positive reaction was not made a condition of entry to the trial, but the test was asked for at entry and "annually thereafter". It was hardly to be expected therefore that comprehensive data at every assessment would be available for analysis and, whilst the percentages in the various "dilution groups" are given in Table XVI, the large numbers *not* tested even at the twelfth and eighteenth months preclude any firm deductions from a comparison of these distributions.

78 of the 90 cases on gold and 83 of the 95 controls were tested at the outset, and the distributions were very similar (first line of Table XVI).

The proportions of positive to negative were 73 to 27 per cent. in the gold group, and 76 to 24 per cent. in the controls. At the eighteenth month the proportion positive had fallen in both groups to 64 and 60 per cent. respectively. But this apparent similarity masks an important change in the make-up of the positives of the two groups. In the gold group there was a decline in the proportion at high positive titres—from 19 per cent. initially, to nil (0 per cent.) at the twelfth month, with a slight rise to 6 per cent. at the eighteenth month, and an increase in the proportion with low positive titres. In the control group, on the other hand, there was a decrease in the proportion with low and moderate positive titres and an increase in the proportion with high positive titres from 19 to 26 per cent. As a result the distributions of the gold and control groups were significantly different at the eighteenth month.

These results must be accepted with some reserve because they are based at the eighteenth month on the results of tests on only 57 per cent. of the gold group and 65 per cent. of the controls.

Change in S.C.A.T. Titres.—Only 26 of the gold group and 36 of the controls had complete records at every assessment from which the time of change from positive to negative or *vice versa* could be established, and these were too few for useful examination.

But 56 patients on gold and 58 controls were tested initially and again at *either* the twelfth or the eighteenth month (or both). For these, the change

TABLE XVI

SHEEP-CELL AGGLUTINATION TEST

PERCENTAGE DISTRIBUTIONS*

Month of Assessment	Group	S.C.A.T.							No. of Patients Tested†	No. of Patients Not Tested
		Negative			Positive					
		−5 to −3	−2 to −1	Total	0 to +1	+2 to +3	+4 to +8	Total		
0	Gold	3	24	27	26	28	19	73	78	12
	Control	8	16	24	30	27	19	76	83	12
1	Gold	10	17	27	23	40	10	73	30	60
	Control	11	25	36	25	22	17	64	36	59
3	Gold	7	33	40	40	17	3	60	30	60
	Control	24	16	40	14	32	14	60	37	58
6	Gold	16	22	38	50	9	4	63	45	45
	Control	14	22	36	28	20	16	64	50	45
12	Gold	16	22	38	35	28	—	63	51	39
	Control	12	23	35	29	25	11	66	52	43
18	Gold	6	30	36	30	28	6	64	50	40
	Control	13	27	40	19	15	26	60	62	33

* The titre regarded as minimal positive at each centre = 0 (see also Section 11 Results: S.C.A.T.).
† Numbers on which the percentages are based.

in S.C.A.T. titres is analysed in Table XVII and can be summarized as follows:

Very Positive Initially (+4 to +8 dilutions above minimal positive value).

There were thirteen on gold and ten controls in this group. Titres in eleven of the thirteen on gold decreased, two of them sufficiently so as to become negative, but only two of the ten controls showed a decrease in titre and in neither did the test become negative.

Moderately Positive Initially (+2 to +3 dilutions above minimal positive value).

This group comprised eighteen on gold and sixteen controls. Titres of eleven of the former decreased, including three who became negative, but in only five of the controls did the titre decrease, and in five the titre rose.

Slightly Positive Initially (0 to +1 dilutions).

Five of eleven on gold became negative; three moved to a higher positive titre.

Seven of seventeen controls became negative; five moved to a higher positive titre.

Negative Initially

Of fourteen on gold, five changed to positive.
Of fifteen controls, six changed to positive.

Thus the evidence is that in the gold group the agglutination titres became less positive to a greater extent than in the control group. It is perhaps worth remarking that this contrasts with the results reported in rheumatoid arthritic patients treated with prednisolone, where there was "a general rise in agglutinating titres amongst those with positive tests" (Joint Committee M.R.C. and Nuffield Foundation, 1959).

Analgesic Tablets Taken (Table XVIII)

At each attendance the numbers of analgesic tablets taken per day together with the type of tablet was assessed retrospectively.

Aspirin or soluble aspirin, taken by the majority of patients, were considered as equivalent.

TABLE XVII

CHANGE IN S.C.A.T. TITRES
(GOLD 56; CONTROLS 58)

S.C.A.T. Dilution Groups* at Start	Group	12th or 18th Month Dilutions*					
		+4 to +8 (very positive)	+2 to +3 (moderately positive)	0 to +1 (slightly positive)	−1 to −2 (slightly negative)	−3 to −5 (moderately negative)	Total
+4 to +8	Gold	2	4	5	1	1	13
	Control	8	2	—	—	—	10
+2 to +3	Gold	—	7	8	3	—	18
	Control	5	6	2	2	1	16
0 to +1	Gold	—	3	3	5	—	11
	Control	2	3	5	6	1	17
−1 to −2	Gold	1	1	2	4	4	12
	Control	—	—	3	3	2	8
−3 to −5	Gold	—	—	1	—	1	2
	Control	—	—	3	1	3	7

* Minimal positive at each centre = 0.
Figures in boxes = No change
Figures to right of boxes = Change to lower dilutions
Figures to left of boxes = Change to higher dilutions

TABLE XVIII

MEAN NUMBER OF ANALGESIC TABLETS TAKEN (PER PATIENT)
(GOLD 90; CONTROLS 95)

Group	Month of Assessment						
	0	1	3	6	12	18	
Gold	8·0 ± ·46	7·4 ± ·48	6·5 ± ·46	5·6 ± ·49	4·6 ± ·48	5·0 ± ·46	S
Control	7·7 ± ·46	7·5 ± ·44	7·3 ± ·44	7·0 ± ·48	7·1 ± ·49	7·4 ± ·53	S

S = Significant difference between the two groups.

Other types (below) were used very infrequently and for counting purposes were converted by the following convenient working rules:

Drug	Tablets of Aspirin
Bufferin, Antoin, Berex, Ce-K-sal ..	1
Co. Codeine, Codis, Veganin	1½
Paynocil	2
Paracetamol, Enseals of Sodium Salicylate	½

Table XVIII shows the mean number of tablets taken per patient at each assessment. Even by such an insensitive index as this, the gold group appeared to fare better. At the start both groups were taking an average of eight tablets per day. Whilst this level remained practically unchanged in the controls, it steadily declined in the gold group to five per day at the eighteenth month and was significantly lower than the level for the controls at the twelfth and eighteenth months.

Radiological Findings

X-ray films of the hands and wrists were available for all patients at entry to the trial, and again at the eighteenth month, except for a proportion of the withdrawals. For those who died or who were not assessed beyond 12 months, only initial films were available. The films were read by a single observer (Dr. Ifor Pennant Williams), who was unaware to which of the groups each patient belonged.

Comparison at the Start of the Trial (Table XIX).—From the initial films the following records were made for each person:

HANDS

(*i*) The number of joints initially affected in any way (20 joints examined per person).

(*ii*) The number of joints unassessable (because of advanced progression, films technically unsatisfactory, or amputation).

(*iii*) The number of joints which had already narrowed.

(*iv*) The number of erosions of any type.

WRISTS

(*v*) An assessment was made of the initial state of each wrist in four grades according to the following rules:

0 *Nil or Slight:* No definite cartilage loss, *i.e.* joint narrowing. Not more than two small erosions.

1 *Moderate:* Definite narrowing and/or a few (2-5) erosions.

2 *Marked:* Extensive narrowing and many erosions.

3 *Unassessable:* Progression too advanced; films technically unsatisfactory, etc.

From these data the indices given below were constructed and compared for the two groups:

TABLE XIX

RADIOLOGICAL COMPARISON OF THE TWO GROUPS AT START OF TRIAL

(*a*) Radiological signs (initially) in joints of the hands

Group	Gold	Control
No. of Patients	90	95
Joints Initially Affected in Any Way (Means—per person)	6·2 ± ·47	5·9 ± ·46
Narrowed Joints (Means—per person)	2·9 ± ·39	2·3 ± ·33
Erosions Present (Means—per person)	7·0 ± ·70	7·0 ± ·69

(*b*) Radiological assessment (initially) of wrists (in four grades)

Wrist	Left		Right		Both		
Grade	Gold (per cent.)	Control (per cent.)	Gold (per cent.)	Control (per cent.)	Grades	Gold (per cent.)	Control (per cent.)
Nil or Slight 0	47 S	62	44 S	68	0, 0	36 S	54
Moderate 1	31	28	34	23	0, 1 (or 1, 0)	19	21
Marked 2	19	9	18	9	1, 1	17	14
Unassessable 3	3	—	3	—	0, 2 (or 2, 0) 1, 2 (or 2, 1)	12	3
					0, 3; 1, 3; 2, 2; 3, 3	17	8

S = Significant difference between the distributions of the two groups.

(1) The mean number of joints of the hands affected in any way (per person).
(2) The number of joints unassessable.
(3) The mean number of joints of the hands which showed narrowing (per person).
(4) The mean number of erosions present (per person).
(5) A distribution of the wrists by severity grades.

In the gold group only six joints of the hands were unassessable initially (four patients with one joint each, and one with two). In the control group only three joints were unassessable (three patients with one each).

Judged by the number of joints affected in any way, or by the number of joints which were narrowed or by the number of erosions present, the two groups as initially constituted were similar at the start of the trial, although there was a slight but not significant excess of narrowed joints in the patients on gold (Table XIX).

These three indices were hardly affected by the exclusion of the withdrawals.

The two groups differed, however, with regard to radiological assessment of the wrists. This arose because a higher proportion of the control patients than of those on gold (68 as against 44 per cent.) were graded for the right wrist as "nil or only slightly affected". For the left wrist the comparable proportions were 62 and 47 per cent. In the gold group 21 per cent. of right wrists and 22 per cent. of left wrists showed marked changes or were so advanced as to be unassessable as compared with only 9 per cent. in the controls.

Taking both wrists together, the higher proportion of the controls with neither wrist more than slightly affected still persisted (controls 54 per cent., gold 36 per cent.). At the same time there were fewer controls with advanced signs in at least one wrist (controls 11 per cent., gold 29 per cent.).

These differences were still apparent when the withdrawals were omitted.

This difference in the radiological severity of rheumatoid arthritis in the wrists is the only factor in which the two groups were found to differ initially. This is not perhaps very important, but illustrates the difficulty of assembling two groups of patients which will not differ in any particular.

Change in Radiological Signs over 18 *Months.*—Progression was assessed by comparing the eighteenth month film with the initial film, and there was recorded on a standardized proforma for each joint of the hands (Table XX):

(*a*) if narrowing had occurred,
(*b*) the number of new erosions,
(*c*) the number of extensions of erosions seen in the initial film.

TABLE XX
RADIOLOGICAL ASSESSMENT OF PROGRESSION OF RHEUMATOID ARTHRITIS IN HANDS

Group			Gold (87)	Control (93)
(1) No. of Assessable Joints		Right	867	929
		Left	869	926
		Both	1,736	1,855
Narrowed Joints	(2) No. of assessable joints not initially narrowed	Right	745	827
		Left	738	816
		Both	1,483	1,643
	(3) No. of joints which subsequently narrowed	Right	61	65
		Left	58	65
		Both	119	130
	(4) Actual joints which narrowed as per cent. of possible number. (3) as per cent. of (2)	Right	8·2	7·9
		Left	7·9	8·0
		Both	8·0	7·9
New Erosions	(5) No. of new erosions which developed	Right	174	198
		Left	155	216
		Both	329	414
	(6) New erosions per assessable joint. (5) ÷ (1)	Right	0·20 ± ·03	0·21 ± ·03
		Left	0·18 ± ·03	0·23 ± ·03
		Both	0·19 ± ·03	0·22 ± ·03
Extensions of Old Erosions	(7) No. of extensions	Right	77	79
		Left	62	55
		Both	139	134
	(8) Extensions per assessable joint. (7) ÷ (1)	Right	·09 ± ·02	·09 ± ·01
		Left	·07 ± ·01	·06 ± ·01
		Both	·08 ± ·01	·07 ± ·01

Note Items 4, 6 and 8 were computed in two ways:
(*a*) by relating, *e.g.* the total new erosions for all patients to the total assessable joints;
(*b*) individually for each patient; and calculating the mean ± S.E. of the resulting series.
The two methods gave almost identical means.

TABLE XXI

RADIOLOGICAL ASSESSMENT OF "PROGRESSION" IN THE WRISTS

Wrist		Right		Left		Both		
Group		Gold (per cent.)	Control (per cent.)	Gold (per cent.)	Control (per cent.)	Grades*	Gold (per cent.)	Control (per cent.)
Progression Grade	Nil 0	29	32	31	25	0, 0	19	14
	Slight 1	40	36	38	35	0, 1	16	20
	Moderate 2	17	17	17	18	1, 1	23	18
	Marked 3	7	9	7	16	0, 2+	4	9
	Very Marked 4	7	7	7	5	1, 2+	18	14
						2+, 2+	20	25
	Total	100	101	100	99		100	100
No. of Wrists		84	92	84	92		83	92

* 0, 0 = Nil in both hands; 0, 1 = Nil in one, Slight in the other, etc.

Progression in each wrist was assessed in five grades (Table XXI) according to the following rules:

0 *Nil:* No change.

1 *Slight:* Small erosion and/or small area of cartilage loss, *i.e.* joint narrowing.

2 *Moderate:* 2-5 erosions and/or narrowing involving 2-3 carpal joints.

3 *Marked:* 4-8 erosions. Narrowing very obvious.

4 *Very marked:* Virtually every joint in the wrist showing narrowing and erosions.

Measurements of progression derived from this information were for each group:

(1) Number of joints narrowed as a percentage of the number which could narrow (Item 4 of Table XX).

(2) Mean number of new erosions per assessable joint (Item 6 of Table XX).

(3) Mean number of extensions of old erosions per assessable joint (Item 8 of Table XX).

(4) Percentage distribution of wrists in the five grades of progression (Table XXI).

Not one of these four indices indicated any difference between the treated and control groups as regards the extent of progression of the disease measured radiologically.

Some consideration was given to the view that the separate comparison of these four radiological signs did not give an adequate picture of the amount of progression in the two treatment groups, since combinations of the four assessments could vary greatly between patients. One patient might for example have three joints narrowed and one wrist showing marked progression. Another might have three joints with extensions of old erosions and one new erosion. Was the overall amount of progression equal in the two cases?

Somewhat diffidently, therefore, an arbitrary method of scoring was devised to combine these indices. The actual and possible scores for each sign are shown below:

Radiological Sign		Score (units per joint)	
		Actual	Possible
(*a*) Joints of Hands	Narrowing	1	1 (but nil if initially narrowed)
	New erosion	2	8 (based on a maximum of four new erosions actually recorded in any joint)
	Extension of old erosion	1	0*
	Total		9 = possible score per joint 90 = possible score for ten joints of each hand
(*b*) Wrists	Slight progression	2	
	Moderate progression	4	
	Marked progression	7	
	Very marked progression	9	9 = possible score for each wrist
	Total		198 = possible score for both hands and both wrists combined

* The possible score for extensions of old erosions ought to depend on the number of erosions initially present in each joint. In the absence of this information no possible score could be determined for extensions.

The overall actual and possible scores for each treatment group are shown in Table XXII, and also the actual score expressed as a percentage of the possible score. This index also showed no real difference between the gold and control groups as regards either hand or both hands combined, nor was there any difference when the wrist assessments were added to those of the hands.

The radiological comparison of the two groups diverges from the clinical assessments: first in that, at the outset, the two groups were similar clinically, but that the wrists of the gold group were more severely affected radiologically; secondly, in that the gold group showed advantage over the controls by every clinical index used, yet there was no difference radiologically.

It is perfectly reasonable to expect such divergences because the clinical and radiological assessments are measuring different aspects of the disease. At the start of the trial the clinical assessment of a specified joint indicated if it was the site of active arthritis at that point of time, whereas the radiological assessment was a measure of the progress of the disease from its onset to the start of the trial (a period varying from 1 to 5 years). It is worth noting that, although (radiologically) the patients in the gold group were the more severely affected as regards the wrists at the start of the trial, yet clinically they showed a greater degree of improvement.

Furthermore, progression of joint changes as judged radiologically does not parallel the clinical progress of arthritis in a joint. A comparison of the clinical and radiological assessments of just one joint (metacarpophalangeal 2) may be cited as evidence. In thirty patients (Gold 18, Controls 12), the features of active arthritis in this joint as assessed clinically disappeared by the sixth month and did not appear again, but the radiological assessment showed no change.

The radiological assessment of healing is difficult, but nevertheless two observers agreed that ten patients showed partial or general healing. Six of these were in the gold group and four were controls.

(12) Discussion

The initial assessment showed the two groups to be comparable and that withdrawals and changes of treatment failed to alter this comparability. The fact that more second courses of control injections were requested than of gold indicates that patient and physician remained genuinely ignorant of the material being used, *i.e.* that the trial remained truly "blind". On comparing the gold-treated and control groups, it is apparent that by all criteria, except radiological progression, the gold-treated group showed a definite and greater degree of improvement than the control group from the third month onwards, and this was maintained until the eighteenth month, that is, over one year after completion of the course of injections, although slightly reduced in degree after the twelfth month. A later assessment will be made after a further one year's follow-up, but to date the advantage clearly lies with the gold-treated group. Although part or all of this improvement may disappear within the next few years, one cannot ignore any form of therapy which gives temporary amelioration of symptoms in a progressive and painful disease, unless the hazards of therapy outweigh the advantages: such hardly seems to have been the case in this trial, though skin reactions were troublesome in a significant number of gold-treated patients and albuminuria was noted on four occasions. Steroid therapy and dimercaprol (B.A.L.), not available to the earlier workers with gold salts, can today effectively reduce the severity of such side-effects and lessen the dangers of this form of therapy.

TABLE XXII

RADIOLOGICAL ASSESSMENT OF "PROGRESSION"
(GOLD 87; CONTROLS 93)

ACTUAL AS PERCENTAGE OF POSSIBLE SCORES

Group		Gold			Control		
Hand		Right	Left	Both	Right	Left	Both
Hands Alone	Actual Score (total for all patients)	486	429	915	540	552	1,092
	Possible Score (total for all patients)	7,688	7,690	15,378	8,265	8,224	16,489
	Actual as per cent. of Possible Score*	6·32	5·58	5·95	6·53	6·71	6·62
Hands and Wrists Combined	Actual Score (total for all patients)	708	647	1,355	783	835	1,618
	Possible Score (total for all patients)	8,444	8,446	16,890	9,008	8,970	17,978
	Actual as per cent. of Possible Score*	8·38	7·66	8·02	8·69	9·31	9·00

* For tests of significance, this index was calculated for each patient and the means and standard errors computed from the resulting series. The means thus obtained differed only slightly from the overall values shown in the Table.

The results of this trial have confirmed the widely-held view that gold salts are of some value in the treatment of early, active cases of rheumatoid arthritis. Radiological improvement could hardly have been expected for, as related previously, radiological examination measures essentially the end result of pre-existing rheumatoid disease up to that point in time. On the other hand the extent of progression during the period of observation was the same in both groups. This suggests that the natural course of the disease had not been altered. If radiological examination 2 years after the end of treatment confirms this observation, it would appear that only symptomatic improvement may have been achieved at the expense of some toxic effects. The fact that the advantage to the treated group as regards subjective well-being had diminished slightly at the twelfth and eighteenth month suggests that the improvement achieved may be of a temporary nature. A similar trend evident in respect of other factors, particularly the erythrocyte sedimentation rate, would lend support to this view. The assessment at the thirtieth month may clarify this point. Until this information becomes available, it would be unwise to assume that the value of chrysotherapy has been established. It remains a fact, however, that 18 months after the start of the trial the group given gold has emerged superior to the control group in all respects except radiological progression. It remains to be seen how long this advantage lasts and whether it can be maintained by further courses of gold or by the prolonged use of small doses of gold at longer intervals.

(13) Summary and Conclusions

(1) 200 out-patients, aged 20 to 64, with active rheumatoid arthritis of 1 to 5 years' duration and previously untreated with gold salts, were divided into two groups. Both were given simple supportive measures, but no corticosteroids, phenylbutazone, or antimalarial drugs were allowed. The treatment group received twenty weekly injections of 50 mg. sodium aurothiomalate (Myocrisin), making a total dosage of 1 g.; the controls received twenty weekly injections of 0·5 μg. of the same substance, a total dose of 0·01 mg.

(2) Assessments were made at the start and at 1, 3, 6, 12, and 18 months in 24 centres in Great Britain. Cases were allocated centrally by a pre-arranged randomized system, the two groups being balanced for age, sex, and duration of disease. Patients and physicians remained ignorant of the material injected, ampoules being identified by the patient's name only.

(3) As assessed by functional capacity (judged by the physician), subjective fitness (judged by the patient), joint involvement, grip strength, number of analgesic tablets taken daily, sheep cell agglutination titre, haemoglobin and sedimentation rate, the gold-treated patients improved to a greater degree than the controls from the third month onwards, and this improvement was still apparent 12 months after the last injection was given, although it was reduced in degree. No such advantage was demonstrated by radiological examination.

(4) Toxic effects, mainly dermatitis, were more than twice as common in the gold-treated group as in the controls and they were also more severe. Dangerous toxic reactions were uncommon.

(5) Gold therapy undoubtedly improved the average clinical condition of the majority of patients in the gold-treated group over a period of 18 months. A further assessment in one year's time will show if this improvement is being maintained.

Our thanks are due to all participants in the various centres for their close co-operation, to the staff of the Department of Medical Statistics in the Welsh National School of Medicine for their invaluable assistance, particularly Miss Kathleen Davies for organizing the routine follow-up of the patients, and also to Messrs. May and Baker for generous supplies of Myocrisin (sodium aurothiomalate) used in both groups of cases throughout the trial.

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Crysothérapie de l'arthrite rhumatismale

Rapport sur des recherches contrôlées et effectuées dans de divers centres arrangées par le Sous-Comité des Recherches du *Empire Rheumatism Council*

RÉSUMÉ ET CONCLUSIONS

(1) Deux cents malades, d'un âge entre 20 et 64 ans, atteints d'arthrite rhumatismale évolutive, présente depuis 1 à 5 ans, non hospitalisés, sans traitement antérieur par des sels d'or, furent divisés en deux groupes. Les deux groupes reçurent un traitement symptomatique, mais on ne leur permit pas de corticostéroïdes, de phénylbutazone ni d'antipaludiques. Le groupe traité reçut des injections hebdomadaires, 20 en tout, de 50 mg. d'aurothiomalate de soude (Myocrisin), c'est-à-dire une quantité totale de 1 gramme; le groupe témoin reçut 20 injections hebdomadaires de 0,5 microgramme de la même substance, faisant une quantité totale de 0,01 mg.

(2) L'évaluation des résultats s'effectua au début du traitement et 1, 3, 6, 12 et 18 mois après, dans 24 centres médicaux de Grande Bretagne. Les malades furent assignés à leurs groupes respectifs par tirage au sort, après un ajustement pour faire les deux groupes correspondre en ce qui concerne l'âge, le sexe et la durée de la maladie. Autant les médecins que les malades ignoraient le moyen employé et les ampoules du médicament ne se distinguaient que par le nom du malade auquel elle étaient destinées.

(3) Selon l'évaluation de la capacité fonctionnelle (jugée par le médecin) de l'état subjectif (jugé par le malade), de l'implication articulaire, de la force de la poigne, du nombre des comprimés analgésiques pris par jour, du titre d'agglutination des globules de mouton, de l'hémoglobine et de la vitesse de sédimentation, l'amélioration des malades traités par des sels d'or fut plus prononcée que celle des témoins à partir du troisième mois, et cette amélioration fut encore apparente, bien que réduite, 12 mois après la dernière injection. Cet effet favorable ne se manifesta pas radiologiquement.

(4) Les manifestations toxiques, surtout la dermatite médicamenteuse, fut plus sevère et plus de deux fois plus fréquente chez le groupe traité par des sels d'or. Des réactions toxiques graves furent peu communes.

(5) Il n'est pas douteux que le traitement par des sels d'or produisit une amélioration de l'état clinique moyen pendant plus de 18 mois. On effectuera une autre évaluation un an plus tard pour voir si l'amélioration se maintient.

Crisoterapia en la artritis reumatoide

Informe sobre una investigación controlada en diversos centros y conducida por el Subcomité de Investigaciones del *Empire Rheumatism Council*

SUMARIO Y CONCLUSIONES

(1) Dos cientos enfermos con artritis reumatoide evolutiva presente durante uno a cinco años, no hospitalizados, de una edad comprendida entre 20 y 64 años, no tratados anteriormente con sales de oro, fueron divididos en dos grupos. Ambos grupos recibieron terapéutica sintomática, pero no se les permitieron ni los corticosteroides, ni la fenilbutazona ni los antipalúdicos. El grupo en él que se llevó a cabo el experimento recibió inyecciones semanales, en número de 20, de 50 mg. de aurotiomalato sódico (Myocrisin) con una dosis total de 1 g.; el grupo testigo recibió otras 20 inyecciones semanales de 0,5 microgramos de la misma substancia, con una dosis total de 0,01 mg.

(2) La valoración de los resultados se realizó a comenzar el tratamiento y a los 1, 3, 6, 12 y 18 meses en 24 centros médicos de Gran Bretaña. Los enfermos fueron asignados a sus grupos respectivos por sorteo, equilibrándose estos grupos en cuanto a edad, sexo y duración de la enfermedad. Tanto los médicos como los enfermos desconocian el fármaco usado y las ampollas administradas no presentaban otra indicación que el nombre del paciente a que iban destinadas.

(3) Evaluada la capacidad funcional (a través del juicio del médico), la sensación subjetiva respecto al estado general (juzgada por el enfermo), la afectación articular, la fuerza para asir, el número de comprimidos analgésicos tomados diariamente, el título de la aglutinación de los eritrocitos de carnero, la hemoglobina y la velocidad de sedimentación, los enfermos tratados con oro mejoraron más que los testigos, majoría que se hacia aparente del tercer mes en adelante y que todavía se apreciaba, aunque disminuida, 12 meses después de la última inyección. Este efecto beneficioso no se manifestó radiológicamente.

(4) Las manifestaciones tóxicas, sobre todo dermatitis, fueron más severas y más de dos veces más numerosas entre el grupo que recibió crisoterapia. Fueron poco corrientes las reacciones tóxicas graves.

(5) Indudablemente la crisoterapia produjo una media mejoría clínica que perduró por un período superior a 18 meses. Posteriores valoraciones que llevaremos a cabo en el plazo de un año nos mostrarán si esta mejoría se mantiene todavía.

See also Appendices I and II (overleaf)

APPENDIX I

STANDARD ASSESSMENT FORM

TREATMENT A or B (leave blank)			DATE OF ENTRY TO TRIAL		
Name of Patient	*Sex* M F / *Age*	*Duration of R.A.* .... mths	*Type of Onset* Acute Non-acute	*Centre*	*Responsible Investigator*

Time of Assessment				Weeks before Start of Trial		Months after Start of Trial													
				−1		0		1		3		6		12		18		30	
Date of Assessment																			
Functional Capacity (1-5) (See p. 102)																			
Patient's Own Estimation of Fitness (1, 25, 50, 75, 100 per cent. well) ..																			
	Side		Right	Left	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.	R.	L.
Joints Involved (see note on p. 104)	Hands	Proximal interphalangeal	1	1															
			2	2															
			3	3															
			4	4															
			5	5															
		Metacarpophalangeal	1	1															
			2	2															
			3	3															
			4	4															
			5	5															
	Wrists																		
	Elbows																		
	Shoulders																		
	Hips																		
	Knees																		
	Ankles																		
	Feet	Metatarsophalangeal	1	1															
			2	2															
			3	3															
			4	4															
			5	5															
	Total Joints Affected																		

Appendix I (cont.)

Strength of Grip (See note on p. 108) ..																		
Haemoglobin Concentration (g. %)																		
Erythrocyte Sedimentation Rate (Westergren) (mm./hr)																		
White Blood Count Total and Differential (per cu. mm.)																		
S.C.A.T. (Give titre if positive) ..																		
Complications in Period																		
Analgesic Tablets (Total number and usual type taken per diem assessed retrospectively)																		
Admission to Hospital (Reason and dates of admission and discharge)																		
Withdrawal (Give reason and date) ..																		

N.B.—Please make sure that *X*-ray films of hands and wrists are done at entry to trial and 18 and 30 months later.

APPENDIX II

Persons and Centres participating in the Trial

Centre	Physician-in-Charge and Other Assessors	Patients
Aberdeen	Dr. Logie Bain, Dr. F. W. Wigzell	8
Bath	Dr. G. D. Kersley	7
Cardiff	Dr. Kenneth Lloyd	8
Droitwich	Dr. J. W. T. Patterson	1
Edinburgh	Dr. J. J. R. Duthie, Dr. J. Knox, Dr. J. M. Bremner	9
Glasgow	Dr. T. N. Fraser, Dr. S. W. Grant	12
Gloucester	Dr. G. R. Fearnley, Dr. W. R. Blatchley	8
Leeds	Prof. S. J. Hartfall, Dr. V. Wright, Dr. R. A. H. Morison, Dr. C. N. Watson	5
London		
Arthur Stanley Institute, Middlesex Hospital	Dr. O. Savage, Dr. J. H. Glyn, Dr. N. Cardoe, Dr. J. J. P. Lomas	12
Chase Farm Hospital, Enfield	Dr. R. M. Mason	7
Postgraduate Medical School, Hammersmith	Prof. E. G. L. Bywaters, Dr. B. Ansell, Dr. J. T. Scott	4
London Hospital	Dr. W. Tegner, Dr. R. M. Mason, Dr. R. R. P. Hayter, Dr. W. G. Wenley	12
Middlesex Hospital	Dr. A. C. Boyle, Dr. D. C. Beatty	4
Prince of Wales' General Hospital, Tottenham	Dr. J. H. Glyn	2
Royal Free Hospital	Dr. A. T. Richardson, Dr. E. A. Kaufmann, Dr. E. D. R. Campbell	9
West London Hospital Medical School	Dr. O. Savage, Dr. M. Joule	6
Westminster Hospital	Dr. F. Dudley Hart, Dr. D. M. Burley	11
Manchester		
Royal Infirmary	Prof. J. H. Kellgren, Dr. A. S. Dixon, Dr. A. J. Popert	10
Withington Hospital	Dr. H. Stuart Barber	9
Newcastle	Dr. Malcolm Thompson, Dr. R. K. McCuish	16
Reading	Dr. R. I. Meanock	15
Sheffield	Dr. G. R. Newns	6
Stoke Mandeville	Dr. A. G. S. Hill, Dr. R. E. H. Partridge, Dr. J. N. McCormick	8
Sunderland	Dr. I. C. Cowan	10
Total No. of Patients		199

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GOUT IN THE MAORI

BY

G. A. Q. LENNANE, B. S. ROSE, AND I. C. ISDALE

From the Queen Elizabeth Hospital, Rotorua, New Zealand

To extend knowledge of the rheumatic diseases epidemiological studies are of considerable importance, and these are of particular interest where disease incidence in different racial groups living side by side can be compared. Such opportunity occurs in New Zealand, especially in the northern part of the North Island where live most of the Maori population. At Rotorua in the centre of this area is the Queen Elizabeth Hospital, the national hospital for rheumatic diseases.

Clinical experiences at the hospital early suggested that the pattern of rheumatism differed in the Maori and European populations; the Maori people appeared to be affected less by rheumatoid arthritis (Rose, 1955), but more by rheumatic fever and gout than the inhabitants of European stock. These apparent differences were considered worthy of further investigation not only because of their intrinsic interest but also because of their possible bearing on aetiological concepts of these diseases. Further, the rate of natural increase of the Maori population is now much greater than that of the non-Maori, and the subject is one of public health importance.

This paper reports one aspect of these investigations: the prevalence of gout in the Maori population. Because the findings are so much at variance with a widely-held opinion that—"gout is much commoner among certain races, *e.g.* the English and German; it is very uncommon among native races" (Hunter, 1956), it is thought worth while to record our results.

Historical Background

Apart from a short visit by the Dutch explorer, Abel Tasman, New Zealand remained unknown to European civilization until its re-discovery by Captain Cook in 1769 (Cook, 1951). At that time Cook found the country inhabited by a Polynesian people who appeared to be remarkably healthy, with a well-organized tribal system. Originally a sea-faring race, the Maori had settled the country in a series of migrations from the central Pacific from approximately the 9th century, culminating with a major settlement in the mid-14th century. An intelligent war-like people with a stone-age culture, they lacked any writing technique, and despite the prodigies of memory of which they were capable, much of the minutiae of their daily life is not known, though traditionally there is little mention of ill health among them (Buck, 1949).

In their voyages of migration, the Maori brought to New Zealand a number of plants and the only land mammals, the Maori dog and the Polynesian rat, which were found in New Zealand at the time of Cook's visit. Despite this lack of mammals, the pre-European Maori diet was essentially sound and well balanced in proteins, carbohydrates, and fats (Turbott, 1940). Water was the only and universal drink. The major sources of protein were the plentiful birds, and the fish and molluscs abounding in lakes, rivers, and sea. Both at catching and preserving these the Maori were expert, and in particular their skill in fishing provoked incredulous admiration from many early explorers (Best, 1929, 1942). Dogs and rats where available formed a less important part of the diet, and the bodies of enemies slain in battle were also consumed. Such cannibalism was morally accepted, being prompted not by lack of animal protein but by motives of revenge and ancient tradition (Cook, 1951; Banks, 1958). The main sources of carbohydrate were the introduced kumara (sweet potato) and the rhizome of the native bracken fern; no refined sugars were available and brewing unknown. Food was cooked by broiling on open

fires or by steaming in Polynesian earth ovens, neither method needing the addition of cooking fat. Sir Joseph Banks, a trained naturalist with Captain Cook, commented on the Maori, both young and old, as being blessed with sound health in a very high degree. Although familiar with gout, he did not record its occurrence, nor indeed that of any other rheumatic illness.

Within the next 50 years, with the advent of traders, sealers, and missionaries, came European diseases, muskets, and alcohol, which combined to produce a rapid disruption of the former way of life and a great deterioration in Maori health (Savage, 1807). In particular, smallpox, measles, scarlet fever, enteric fever, tuberculosis, and gonorrhoea led to great mortality, the last three diseases remaining common until very recent times. In evidence submitted to Commissioner Bigge's inquiry in 1821, Dr. Fairfowl stated that the most prevalent diseases were pneumonia, inflammation of the bowels, dysentery, rheumatism, ulcers, and venereal disease, but did not further specify the type of rheumatism (Fairfowl, 1908).

Disease, the wars of the 1860s, and the subsequent dispossession of much of their best land led to a marked decline of the Maori people; not only were their numbers decimated, but the survivors were also disorganized and undernourished. Newman (1880), in a valedictory presidential address to the Wellington Philosophical Society, commented on their "sparse diet of fern root and dried eels". He mentioned as common, "rheumatism in all its forms, consumption, and scrofula", but specifically stated that "no Maori ever had gout". That nutrition was then unsatisfactory is indicated by his mention of "Maori leprosy", a malnutrition syndrome seen most frequently among the poorer tribes, which responded rapidly to improved food and care.

With the introduction of domestic animals, potatoes, and cereals, there was a rapid change in diet. Fish and birds were replaced by a smaller amount of tinned and fresh meats and there was a marked increase in the amount of carbohydrate, particularly white sugar, potatoes, and cereals. The Maori early acquired a lasting fondness for beer. Milk and cheese consumption was always low among them, though as much butter was eaten as economic status allowed (Turbott, 1940).

In 1902, Dr. A. S. Wohlmann was appointed as the first medical officer to the Government Sanatorium at Rotorua in the centre of the hot mineral spring area. In his work on the mineral waters of New Zealand (Wohlmann, 1914), he recorded gout or "goutiness" in 16 per cent. of his Sanatorium cases, and in 30 per cent. of his private cases. A later medical officer at the same institution, Dr. A. T. M. Blair, commented that many of the patients with gout would later have been classified as suffering from "fibrositis" (Blair, 1951). Nevertheless, Wohlmann mentioned two Maori patients exhibiting tophi, though he subsequently commented on the rarity of both acute and tophaceous gout in the Maori race (Herbert, 1921). This is the earliest report of gout in a Maori.

Until the last 25 years the economic status of the Maori remained low, and in this period the usual diet was low in first-class protein, vitamins, and protective foods.

The old methods of cooking had been supplanted by frying or baking in electric or coal ranges and this, with the Maori preference for fat meat, led to an increase in fat intake. In 1942, a dietary survey (McLaughlin and Wilson, 1945) was conducted among Maori families of the Arawa tribe. At that time, with full employment and generous children's allowances, the Maori was in a much more favourable financial position than ever before. The survey showed that, compared with the basic wage-earning European group, less dairy produce, fruit, and vegetables but more carbohydrates were eaten, both groups having a high meat intake. Since then no further survey has been done, but it is the general belief that these dietary patterns remain qualitatively unaltered. By European standards the total quantity of food consumed would be considered generous.

Surveys of Rheumatic Disease in the Maori Population

Material and Methods.—Since 1956 we have conducted two independent surveys of the prevalence of rheumatic disease among the Maori. In these surveys the definition of "Maori" has followed current New Zealand usage to include all those people of at least half Maori blood who consider themselves to be members of the Maori community. Only a portion of such persons are of completely unmixed Polynesian ancestry. In 1871, the darkest period of the Maori race, there were approximately 37,520 Maori; in 1896, 42,113; in 1921, 55,000; and in 1936, 82,326. In 1956 the Maori composed 137,341 of the total New Zealand population of 2,174,062. These figures give some idea of the present rate of population increase.

First Survey (Rose, 1956).—This was conducted by one of us (B.S.R.), with the help of a medical social worker and in conjunction with officers of the

Maori Affairs Department, in a tribe of comparatively "pure" blood. At the time of a personal interview with a Maori Affairs Officer, a questionnaire was completed for all the adults of this tribe (the Whanau-a-apanui), a rural community living in the most easterly part of Auckland Province.

All those with a history or symptoms of rheumatism were examined for peripheral arthritis. Gout was suspected in those who gave a history of episodic acute arthritis, usually peripheral and asymmetrical, characterized by severe pain and swelling which subsided completely, and responding to colchicine when exhibited. Blood samples were obtained when possible in suspected cases of gout, and serum uric acid level and erythrocyte sedimentation rate were estimated, and a sheep cell agglutination test (S.C.A.T.) performed. It was not possible to have many *x* rays done. Diagnosis was made on the typical history and clinical findings, confirmed by a raised serum uric acid level. All serum uric acid levels were determined photometrically by Beale's modification of Folin's method (Beale, 1954). The cutting line for this method is at 6 mg. per cent. for women and 7 mg. per cent. for men. Hyperuricaemia was not regarded as sufficient evidence of gout in the absence of clinical history or of typical physical signs (Goldthwait, Butler, and Stillman, 1958).

Of 462 Maori adults in the tribe, 88 made complaint of rheumatism. The results of the examination are shown in Table I; 22 were found to be suffering from clinical gout, and a further three with hyperuricaemia were possibly gouty. No classical rheumatoid arthritis was seen, although there was a group of fourteen patients with a history of recurrent arthritis or arthralgia without diagnostic signs.

TABLE I

WHANAU-A-APANUI SURVEY, 1956

No. of Persons	Interviewed	462
	Examined	88
Rheumatic Conditions	Classical clinical gout	
	(*a*) confirmed by hyperuricaemia 20	
	(*b*) blood not examined 2	22
	Possible gout with hyperuricaemia	3
	Definite rheumatoid arthritis	0
	Recurrent arthralgia (not further defined)	14
	Degenerative joint disease and mechanical derangement	20
	Extra-articular conditions	26
Nonrheumatic Disorders		3

In the 22 cases of clinical gout, the serum uric acid was determined in all but two, and all were found to be raised (see Table II).

TABLE II

SERUM URIC ACID LEVELS IN 22 CASES

Case No.	Sex	Age (yrs)	Serum Uric Acid	S.C.A.T.
1	M	33	11·5	·
2	M	36	11·10	−ve
3	M	68	10·45	·
4	M	44	10·25	·
5	M	67	10·05	·
6	M	37	9·5	−ve
7	M	51	9·4	·
8	M	65	9·2	−ve
9	M	66	9·2	·
10	M	52	9·05	−ve
11	M	42	8·6	−ve
12	M	50	8·45	·
13	M	79	8·3	·
14	M	38	7·95	·
15	M	65	7·85	−ve
16	M	58	7·2	−ve
17	M	48	·	·
18	M	41	·	·
19	F	60	10·3	·
20	F	52	9·3	·
21	F	53	7·4	·
22	F	56	7·35	·

Second Survey.—This was carried out in 1957-58 by the staff of the Queen Elizabeth Hospital and the School of Social Sciences of Victoria University, Wellington. A 1 : 12 random sample was taken of both the Maori and non-Maori adults of Rotorua, a country town of approximately 15,000 people. Most of the Maori in the area are members of the Arawa tribe, who through long friendly association with European settlers are a less pure and homogeneous section of the Maori people than the subjects of the 1956 survey. The survey was performed by personal interview, at which time 827 questionnaires were completed. 361 persons complaining of rheumatic symptoms were subsequently examined clinically, and in most cases the erythrocyte sedimentation rate was estimated, a sheep-cell agglutination test was carried out, and standard *x* rays were taken of the hands and feet. Serum uric acid determinations were done only in those cases in which the presence of gout was considered probable on clinical grounds. The relevant diagnostic findings are shown in Table III (opposite); the detailed methodology and findings of this survey will be reported later (Rose and Isdale, in preparation).

Criteria for the diagnosis of gout were the same as those in the preceding 1956 survey with more extensive use of *x* rays. Of 641 non-Maori subjects, only two sufferers from gout were found, while of the 186 Maori subjects, five were gouty, a significant difference ($\chi^2 = 9{\cdot}699$; $p < 0{\cdot}01$).

All seven patients with gout had a raised serum uric acid level (Table IV, opposite). On this occasion some definite rheumatoid arthritis was found among the Maori subjects, but much less than among the non-Maori (see Table III).

TABLE III

ROTORUA SURVEY, 1957-58

Race		Maori	Non-Maori	Total
No. of Persons	Interviewed	186	641	827
	Examined	66	295	361
Rheumatic Condition	Classical Clinical Gout	5	2	7
	Definite Rheumatoid Arthritis	2	43	45
	Probable Rheumatoid Arthritis	4	35	39
	Degenerative Joint Disease and Mechanical Derangement	—	—	77
	Miscellaneous, including possible Rheumatoid Arthritis and Rheumatic Fever	—	—	74
No Rheumatic Diagnosis		—	—	119

TABLE IV

URIC ACID LEVELS IN SEVEN CASES
ROTORUA SURVEY, 1957-58

Case No.	Sex	Age (yrs)	Race	Uric Acid Level	S.C.A.T.
1	M	41	European	8·45	−ve
2	M	51	European	8·1	−ve
3	M	48	Maori	7·9	−ve
4	M	49	Maori	7·6, 11·4	−ve
5	M	40	Maori	8·5	−ve
6	M	37	Maori	8·7	−ve
7	M	23	Maori	9·3	−ve

While the prevalence of gout among the Whanau-a-apanui tribe of the East Coast was found to be higher than among the Arawa people of Rotorua, this difference is not significant ($\chi^2 = 1{\cdot}428$; $0{\cdot}50 > p > 0{\cdot}30$). A high level of significance is achieved when the prevalence in the combined tribes is compared with the non-Maori population of Rotorua ($\chi^2 = 21{\cdot}77$; $p < 0{\cdot}001$). In each survey group, men were much more frequently found to be gouty (Table V), an expected observation (Hench, Bauer, Dawson, Hall, Holbrook, Key, and McEwen, 1940).

Discussion

It is widely held that gout is rare among native races (Hench and others, 1940; Brugsch, 1957; Perlman, Bernstein, Maslow, and Scatliff, 1953). The historical evidence supporting this opinion in the case of the Maori of past generations has been briefly reviewed. That such a view is no longer true among the present Maori community has been clearly demonstrated by these surveys. Among another Pacific race, the Filipinos, a high and probably increasing incidence of gout has recently been reported (Decker and Lane, 1959). In the United States, Nathan, Kubota, and Turnbull (1953) reported an incidence of gout of 0·04 to 0·2 per cent. among Negroes admitted to the Cook County Hospital between 1944 and 1952, compared with an incidence of 0·06 to 0·1 per cent. among the white patients at the same hospital.

Among the patients with gout treated at this hospital, the Maori patients show certain minor clinical differences. Tophi are less common, and when present are never large. Impaired renal function is occasionally found, but little work on the renal pathology has been possible because of the characteristic difficulty in obtaining permission for

TABLE V

INCIDENCE OF GOUT IN TWO SURVEYS

Survey			Sex		Total
Centre	Race	Date	Male	Female	
Whanau-a-apanui Tribe	Maori	1956	18 of 219 8·2 per cent.	4 of 243 1·6 per cent.	22 of 462 4·7 per cent.
Rotorua	Arawa Tribe Maori	1957-58	5 of 83 6·0 per cent.	0 of 103 0 per cent.	5 of 186 2·7 per cent.
	Non-Maori	1957-58	2 of 296 0·7 per cent.	0 of 345 0 per cent.	2 of 641 0·3 per cent.

autopsy or biopsy from the Maori. Associated hyperpiesia is not infrequent. No estimations of total uric acid pool have yet been done. In their response to the treatment of both acute and chronic gout, Maori patients differ in no way from non-Maori subjects, except that, to be effective in long-term treatment, probenecid is needed in a dosage of 2 g. daily rather than the more usual 1-g. dosage used for non-Maori patients with gout. Not uncommonly there is a past history of gonorrhoea, and in cases showing a positive gonococcal complement-fixation test, treatment with parenteral penicillin combined with pyretic baths has value as an adjunct to the usual gout treatment.

Historical evidence quoted above makes it probable that gout was uncommon, if seen at all, among the Maori in the days before their discovery by Europeans and until the present century. There seems little doubt that there has been a genuine and marked increase of gout in the Maori, and while it is difficult to be certain when this increase occurred, it has been most marked in the last 20 to 30 years.

The incidence of clinical gout is at least partially genetically determined, and in Caucasian races a reservoir of potentially gouty subjects exists. Experience in Germany (Zöllner, 1957) during and after World War II shows how the amount of clinically obvious gout may fluctuate with the general state of nutrition of the population. Acute classical gout, notoriously prevalent among the nobility and gentry in the Regency period, is steadily diminishing in England (Thompson, 1938), but is being recognized more frequently in the United States (Hench and others, 1940); changing economic status may be a factor in this transatlantic shift. The results of the surveys of the Maori reported above show that the genetic defect preceding clinical gout is present in the race, as much in the East Coast tribe with minimal racial admixture as in the less racially pure Arawa people. This strongly suggests that, though clinical gout was not earlier recognized, the Maori has always been potentially gouty. It is of interest in this context that gout is not seen among the Polynesians living in the New Zealand dependencies in the Pacific (McCarthy, 1956). These island peoples, whose anthropologic and blood group characteristics (Simmons, Graydon, Semple, and Taylor, 1951) closely resemble those of the Maori, still live to-day in a culture not unlike that of the pre-European Maori, with a simple diet consisting largely of fish and root vegetables. It will be of great interest to see whether the incidence of gout rises in these people with any future improvement of economic status.

Failure by early observers in New Zealand to describe gout may have been due in part to underdiagnosis, though the background, training, and worth of those observers and the very magnitude of the incidence among the Maori to-day, makes it certain that there has been a very real increase in frequency. In the absence of a significant genetic change, other factors must be sought to explain this, and of these, the marked change of diet and cooking method is probably the most important. This increase of prevalence has appeared at a time of markedly increased material prosperity and life expectancy: to-day the Maori who earns well spends freely, particularly on rich foods, beer, and other creature comforts.

Summary

Population surveys show a much greater prevalence of gout among the Maori people of New Zealand than among people of European stock. Historical evidence strongly suggests a real and recent increase in incidence. It is suggested that the marked economic and dietary changes in the Maori cultural environment in the last two hundred years could sufficiently explain this without postulating any alteration in the necessary genetic constitution.

We wish to acknowledge the most courteous and generous reception to our survey teams by the Maori people, and the help given by our own social workers, Mrs. Welsh and Miss Newcombe, and the staffs of the Department of Maori Affairs and the School of Social Sciences of Victoria University, Wellington.

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La goutte chez les Maoris

RÉSUMÉ

Des enquêtes effectuées en Nouvelle Zélande ont révélé une plus grande fréquence de la goutte chez les Maoris que chez les personnes d'origine européenne. Des données historiques indiquent fortement que cette fréquence augmentée est réelle et récente. On pense que des changements alimentaires et économiques marqués dans l'ambiance culturelle des Maoris au cours de derniers deux cents ans expliquent ce fait suffisamment, sans qu'il soit nécessaire de postuler une altération de la constitution génétique.

La gota en los Maoríes

SUMARIO

Censos en la Nueva Zelandia revelaron una mayor frecuencia de la gota en los Maoríes que en las personas de origen europeo. Datos históricos sugieren fuertemente que este aumento es auténtico y reciente. Se cree que cambios alimentarios y económicos en el ambiente cultural de los Maoríes en los últimos dos cientos años bastan para explicar este hecho, sin necesidad de postular una alteración de la constitución genética.

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RENAL AMYLOID

A REPORT ON ELEVEN CASES PROVEN BY RENAL BIOPSY

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Amyloid deposition in the kidneys and other organs represents an intriguing anomaly. The whole problem, with a discussion of so-called primary and secondary amyloidosis, has been fully reviewed in recent years (Symmers, 1956).

Amyloidosis occurs secondarily to a variety of chronic diseases, in particular those with chronic suppuration, but also in association with such conditions as rheumatoid arthritis and multiple myelomatosis. Since the introduction of many potent antimicrobial agents, such chronic infections are becoming uncommon, and a higher proportion of cases of secondary amyloidosis will be found in association with other conditions. The association of amyloid with rheumatoid arthritis is the most striking. Fingerman and Andrus (1943) found some amyloid deposits in thirteen of 61 autopsies on patients with rheumatoid, and Teilum and Lindahl

Case No.	Sex	Age at Time of Renal Biopsy (yrs)	Date of Renal Biopsy	Date when Proteinuria First Found	Renal Functional Data		
					Date	Blood Urea (mg./100 ml.)	Urea Clea (ml./mi
1	F	28	17.9.57	July, 1949	January, 1949 November, 1952 January, 1954 June, 1959	35 40 55 60	45 30
2	M	31	17.9.57	July, 1957	September, 1957	35	54
3	F	37	22.11.57	August, 1957 No proteinuria +ve October, 1957	October, 1957 July, 1959	170 300	
4	M	30	12.2.58	December, 1954	March, 1958 January, 1959 July, 1959	55 52 46	
5	F	46	19.11.58	September, 1958	November, 1958	38	45
6	M	60	31.12.58	1953	November, 1958 September, 1959	80 80	20
7	M	38	4.2.59	December, 1958 (1 urine specimen, ? 1931)	February, 1959 November, 1959	30 40	(Creatini 92 m
8	M	59	17.4.59	January, 1959	January, 1959	50	20
9	M	54	22.5.59	April, 1959	April, 1959	47	22
10	M	35	8.8.59	June, 1956	June, 1956 November, 1957 March, 1959 August, 1959	30 80 63 86	60
11	F	26	2.10.59	September, 1958	June, 1959	38	

(1954) claimed an incidence of 60 per cent. in autopsy material. Fearnley and Lackner (1955) made a clinical diagnosis of amyloid in eight of 183 patients with rheumatoid arthritis seen during a single one-year period.

In 220 successful renal biopsies, eleven cases of amyloid infiltration have been found. This surprisingly high incidence has led us to document these patients. Apart from questioning the generally held belief that amyloid disease is now a rarity, some interesting problems are posed by the long interval in some cases between establishing the presence of amyloid infiltration of the kidneys and any possible causative underlying disease.

Brief clinical histories are given below. Table I sets out some of the salient features of the eleven cases; there is obviously no proof of the relationship of any underlying disease to the amyloid deposition.

Case Reports

Case 1, a female aged 28.—In 1939 (at age 11) an operation was performed for osteomyelitis of the left hip. In 1940 there was a recurrence of the abscess in the same region and she was put in plaster; the left hip was fully ankylosed by December, 1941. In 1942 the sinus in the left groin broke down. In 1943 the head of the right humerus was explored and the sequestrum removed. Between December, 1944, and May, 1946, she had four recurrences of abscess formation in relation to the left hip. In December, 1947, the left hip was drained and she was treated with penicillin. In January, 1949, two-thirds of the ala of the left ilium which contained two sequestra were removed. In July, 1949, proteinuria was found at a routine medical examination. Chronic nephritis was diagnosed, hypertension slowly developed, and progressive impairment of renal function occurred. The hypertension became severe with diastolic levels up to 150 mm. Hg in 1954, when occasional small haemorrhages were present in the fundi.

After the episode of severe hypertension in 1954, energetic hypotensive therapy was instituted; the blood pressure has been well controlled and renal function has remained approximately static. She leads a full normal life and gave birth to a normal live child in 1957 (by Caesarean section), the year in which the renal biopsy was performed. There has been no evidence of active osteomyelitis since 1949. She was last seen in December, 1959, when proteinuria was still present.

Interval between Last Evidence of Activity of Possible Underlying Lesion and Renal Biopsy	Highest B.P. (mm. Hg)	Heaviest Proteinuria (g./24 hrs)	Maximum Oedema (0 to ++++)	Lowest Plasma Albumin (g./100 ml.)	Highest Serum Cholesterol (mg./100 ml.)
8 years (Osteomyelitis)	240/150	3·0	0	3·5	123
13 years (Osteomyelitis)	150/102	1·0	0	3·2	184
5 months (Osteomyelitis)	230/130	8·0	0	3·3	280
3 years (Pulmonary tuberculosis)	180/100	12·0	0	4·0	212
Still active (Rheumatoid arthritis)	130/80	4·0	0		211
40 years (Osteomyelitis)	150/90	20·0	+	2·0	125
25 years (Osteomyelitis) 1 year (Ulcerative colitis)	130/80	15·0	+++	1·2	160
Still active (Purulent bronchiectasis)	100/65	14·0	0	3·0	330
None	160/110	7·5	+	2·5	252
10 years ...nary and genital tuberculosis)	180/120	20·0	++	2·4	283
...0 years (Bronchiectasis)	140/75	5·3	0	3·1	—

Case 2, a male aged 31.—In 1929 (at age 3) he fractured the right arm, and this was followed by infection and metastatic osteomyelitis in the left orbit and cheek, right ring finger, right elbow, and cervical spine. He was extremely ill for 6 months but then gradually improved and developed normally. However, there was an intermittent discharge from sinuses on both sides of the neck, which continued until age 17. He was admitted to hospital in August, 1957, with a 2-year history of epigastric pain, not related to meals but relieved by alkalis.

Examination.—He was fairly healthy looking; there was limitation of neck movements in all directions with healed sinuses on both sides of the neck, right elbow, left forearm, and right cheek. There was shortening of the right ring finger, and the right elbow was ankylosed. The blood pressure was 135/100 mm. Hg. There was an otitis media with some discharge. There was no oedema. Proteinuria was present. *X* rays showed complete fusion of all cervical vertebrae from below the axis. A barium meal showed a traction diverticulum at the level of the tracheal bifurcation and the presence of a duodenal ulcer. Renal biopsy was performed at this time.

No follow-up was possible as contact with the patient was lost.

Case 3, a female aged 37.—In 1932 (at age 12) the patient was treated for osteomyelitis of the sacrum and was in hospital for 2 years. In addition there was an intermittent discharge of pus from the rectum.

1941: In hospital with presacral abscess.
1942: Osteomyelitis of sacro-iliac joints.
1943: Normal pregnancy. No proteinuria.
1947: Normal pregnancy, except for transient urinary infection. Blood pressure 120/80 mm. Hg.

1957 *June*: Febrile episode with pus discharging from the rectum.

September: Urine stated to be free from protein.

October: Admitted to hospital with anaemia and renal failure at which time proteinuria was found and renal biopsy performed.

Examination.—The patient was pale and thin; the blood pressure was 150/80 mm. Hg. There was no oedema. There was a well-healed scar over the right sacro-iliac joint. Sigmoidoscopy showed no significant abnormality.

1959 *June:* She was re-admitted to hospital because of persistent vomiting and headaches; the blood pressure 230/130 mm. Hg, and haemorrhages and exudates were present in the fundi. She developed a cerebral haemorrhage and died shortly afterwards.

Case 4, a male aged 30.—In August, 1945 (at age 17) pulmonary tuberculosis was diagnosed and he was treated with rest in bed.

1951 *March to October:* He was treated with P.A.S.

1954 *February:* He started treatment with streptomycin and isoniazid.

December: Left thoracoplasty was performed, and proteinuria was noticed post-operatively.

1955 *July:* He had a further operation after which proteinuria increased. The blood pressure at this time was said to be slightly raised.

1957 *March:* The blood pressure was 135/80 mm. Hg; there was no proteinuria.

December: He was referred to another hospital because of proteinuria. At this time the blood pressure was 150/100 mm. Hg; there was slight ankle oedema and old thoracoplasty. There had never been any micturition symptoms, nor any nocturia. There had been no discharge at any time from the operation site.

1958 *January:* He was admitted to hospital.

Examination.—He was a rather thin but healthy-looking man. There was no oedema and no clubbing. The venous pressure not raised. The blood pressure was 180/96 mm. Hg. The urine contained large quantities of protein with a few white cells and epithelial cells in the sediment.

Since the renal biopsy (February, 1958) he has remained fully active; there has been no deterioration in renal function up to July, 1959, although proteinuria still persists.

Case 5, a female aged 46.—In 1942 (at age 30) the patient started having joint pains, affecting the shoulders, wrists, hands, and knees. She received physiotherapy with only slight improvement. In 1954 the symptoms became considerably worse and she presented the typical appearances of rheumatoid arthritis. For the following year she had monthly injections of bismuth but the arthritis continued to progress. In January, 1958, she developed an erythematous rash on the face. No L.E. cells were found in the peripheral blood and the urine was said to be normal. She was started on chloroquine therapy, which was continued until October, 1958. In September, 1958, proteinuria was found for the first time.

Examination (November, 1958).—She was small and wasted with gross limitation of many joints and typical rheumatoid appearance of the hands. The blood pressure was 130/80 mm. Hg. There were no abnormal physical signs in any other system.

Following renal biopsy in November, 1958, she has shown some deterioration in her general condition, although there is some diminution in proteinuria.

Case 6, a male aged 60.—In November, 1958, he developed bronchopneumonia which was treated with penicillin and tetracycline. A heavy proteinuria was found and because of this he was admitted to hospital. In 1953 he had been in another hospital with a chest infection and proteinuria had been noted at that time; there had been no urine examination between that time and the recent illness. At no time had there been any

history of swelling of the legs or any other part of the body. In 1917 (at age 17) he had sustained a gunshot wound of the left knee with local bone infection; arthrodesis of the knee was performed and he was discharged after 9 months. There has been no trouble with the knee since that time.

Examination.—He was healthy looking. There was an old arthrodesis of left knee with healthy scars above the knee joint, and no evidence of a discharging sinus. The blood pressure was 120/80 mm. Hg. There was no oedema. *X*-rays showed arthrodesis of the left hip and distortion of the lower femur, but no evidence of sequestra. There was no pulmonary lesion.

Since the stay in hospital from November, 1958, to January, 1959, when renal biopsy was performed, there have been several episodes of oedema, but when he was last seen in October, 1959, he was well and showed no oedema. There has been no rise in blood pressure but proteinuria persists unaltered.

Case 7, a male aged 38.—In 1931 (at age 10) he had osteomyelitis of the right hip, which was drained surgically; the acute lesion subsided and a bony ankylosis of the hip joint occurred. There had been no further evidence of any active bone lesion at any time, but although the joint was mobile, the position was bad and in August, 1955, a subtrochanteric osteotomy was performed. Since that time mobility has been excellent and he has been able to run and ride a bicycle. Ever since discharge from hospital at the age of 13, following the episode of osteomyelitis, there have been periodic episodes of asthma. In 1949 he had a severe attack of persistent diarrhoea and ulcerative colitis was diagnosed. He remained in hospital for 3 months and made a good recovery. In 1951 there was a further attack of ulcerative colitis which again cleared up with rest in bed. In October, 1957, there was a further severe recurrence of ulcerative colitis and he was treated for 3 months with cortisone, at first 150 mg. and subsequently 100 mg. daily. While taking cortisone he suddenly developed gross oedema which was affected neither by stopping the cortisone, nor by mercurial diuretics. There is no record of any urine test at that time. In August, 1958, there was an attack of right lower lobe pneumonia, which resolved rather slowly. In October, 1958, he had herpes zoster in the right second lumbar region and he was admitted to hospital on December 3, 1958, with fever and evidence of a right lower lobe pneumonia.

Examination.—He was a rather small pale man, febrile, with tachycardia and dyspnoea, and moderate oedema up to the knees. The blood pressure was 130/80 mm. Hg. There were crepitations and poor air entry at the right base. The right hip was ankylosed, but painless, with no evidence of any discharging sinus. Heavy proteinuria was present.

Following renal biopsy on February 4, 1959, he has kept very well and has been doing full work. The blood pressure has not risen, the plasma protein pattern has improved, and proteinuria has diminished from approximately 1 g./100 ml. in January, 1959, to 200 mg./100 ml. in November, 1959. At this time the maximum urinary specific gravity was 1,030 and the blood urea 40 mg./100 ml.

Case 8, a male aged 59.—He had an attack of pneumonia as a child and had always been liable to coughs and colds and general ill-health since that time. During the 1914-1918 war he was gassed; this was not followed by any marked deterioration in health. In 1942 he had an attack of pneumonia and ever since this time had had recurrent episodes of chest infection, and moderate amounts of yellowish sputum almost continuously. Examination and culture of sputum have been repeatedly negative, and there was no history of any pleural involvement. He was admitted to hospital in April, 1959, with an exacerbation of his chronic symptoms.

Examination.—He was fairly well-looking, and not cyanosed. There was clubbing of fingers and toes, but no oedema. The blood pressure 100/65 mm. Hg. There was markedly diminished movement of the left chest, and generalized rales over the left lung. *X*-ray of the chest showed diffuse cystic bronchiectasis. The urine contained large amounts of protein varying from 5 to 14 g. per 24 hrs. Proteinuria had been discovered in January, 1959.

No follow-up has been possible since the renal biopsy on April 17, 1959.

Case 9, a male aged 54.—For 20 years the patient had had repeated episodes of vague abdominal discomfort, lasting about 10 days and recurring 2 or 3 times a year. The episodes were not usually associated with vomiting, diarrhoea, or constipation, nor with any severe pain. He was admitted to hospital on May 19, 1959, following a similar episode, in which abdominal pain was associated with vomiting and diarrhoea. This attack passed off after 3 days. Never at any time had he complained of any micturition symptoms. Apart from some tightness of his shoes during the last 6 months, there had been no other significant symptoms.

Examination.—He was an alert and healthy-looking man. There was slight oedema of the ankles, the venous pressure was not raised, and the blood pressure 160/110 mm. Hg. There were no other abnormal physical signs. The urine contained considerable quantities of protein.

Following renal biopsy in May, 1959, he has remained fairly well. Some oedema of the legs has been present and proteinuria persists.

Case 10, a male aged 35.—In 1946 (at age 22) pulmonary tuberculosis was diagnosed and a pneumoperitoneum was maintained for 18 months. In 1949, bilateral orchidectomy for genital tuberculosis was performed and a two-stage thoracoplasty carried out. He remained well until June, 1956, when proteinuria was discovered, but renal function was normal and a

Congo red uptake test and a gum biopsy failed to confirm a diagnosis of amyloidosis. By November, 1957, the proteinuria had increased markedly but no oedema was present. At this time amyloid was diagnosed by liver biopsy.

In August, 1959, he was admitted to hospital again with upper abdominal pain and nausea. The blood pressure had risen to 180/120 mm. Hg and oedema was present. There was no evidence of an active tuberculous lesion and the blood urea was only slightly higher than 2 years before.

A renal biopsy was performed on August 8th, 1959, to exclude a renal lesion other than amyloid.

Case 11, a female aged 26.—In 1936 (at age 3) bronchiectasis was discovered following a severe attack of measles.

1948 *September:* A bilateral Caldwell-Luc operation was performed.

October: A right middle and lower lobectomy was performed.

1949 *October:* The left lower lobe and lingula were removed.

1953*:* Both tonsils were removed.

1956 *August:* She had a normal full-term delivery.

1958 *August:* She had an appendicectomy, and the urine at this time was free of protein.

September: Proteinuria was discovered during a pregnancy and this persisted after a normal full-term delivery in February, 1959.

Since 1950 she has had intermittent chest infections controlled by tetracycline, but she produces moderate amounts of greenish sputum even during remission.

1959 *June:* She was admitted to hospital for investigation of proteinuria.

Examination.—She appeared healthy; there was no oedema and the blood pressure was 140/75 mm. Hg. The liver was felt two finger-breadths below the costal margin. The urine contained up to 5·3 g. protein per 24 hrs. Suspecting amyloidosis, a liver biopsy and gum biopsy were performed, neither of which showed amyloid. The renal biopsy performed 4 months later, however, showed amyloid.

Pathological Findings

Renal biopsy was performed and sections prepared as described in a previous publication (Joekes, Heptinstall, and Porter, 1958). Table II shows the distribution and extent of the amyloid infiltration in the eleven biopsies. Methyl violet was used as a stain for amyloid. The main distribution is in the capillary tufts of the glomeruli and was present in

TABLE II

ANALYSIS OF PATHOLOGICAL FINDINGS

Case No.	No. of Glomeruli	Glomerular Involvement by Amyloid	Amyloid in Vessels (0 to ++)	Tubular Loss	Amyloid in Medulla (0 to ++) (−signifies no medulla in specimen)
1	18	9/10 Atr. 1/10 Mod.	+	Severe	−
2	14	1/3 Atr. 2/3 Min. or Normal	+	Slight	−
3	20	2/3 Mod. 1/3 Min.	++	Severe	−
4	35	1/3 Atr. 2/3 Mod.	+	Slight	−
5	20	1/2 Min. 1/2 Normal	++	None	++
6	28	1/10 Atr. 9/10 Min.	+	Slight	+
7	64	9/10 Atr. 1/10 Mod.	+	Very severe	+
8	12	10/10 Mod.	+	Slight	+
9	50	1/2 Sev. 1/2 Mod.	+	Moderate	−
10	28	1/10 Sev. 9/10 Mod.	+	Slight	+
11	25	3/10 Atr. 7/10 Mod.	+	Slight	+

Abbreviations in Col. 3*:* Atr.—small tufts with only faint staining for amyloid and often with surrounding rim of collagen.
Min.—minor changes—small local thickenings of capillaries in tuft.
Mod.—moderate changes—more extensive nodular thickenings of capillaries in tuft.
Sev.—severe changes—considerable amyloid replacement of walls of tuft capillaries.

this site in every case, involving every glomerulus in the specimen in nine out of the eleven biopsies. The earliest change consisted of small thickenings of the capillary basement membrane, sometimes affecting many. At a later stage the thickenings were larger and more nodular, the nodules having a "soft" diffuse eosinophilic appearance (Fig. 1). In some cases the nodules were more compact and bore a great resemblance to the nodules seen in diabetic glomerulo-sclerosis but differing in that they gave a strongly positive reaction for amyloid. A more advanced form of change consisted of small reduced tufts with few nuclei and showing either ghosts of basement membranes which stained for amyloid in a rather patchy way or small clumps of amyloid. This weakening and disappearance of staining reactions for amyloid in severely affected glomeruli has been noted by Fahr (1925) and Noble and Major (1929). These atrophic tufts frequently showed a surrounding mantle of collagen (Fig. 2). One case showed a pronounced diffuse amyloid thickening of the capillary basement membranes, which in places was so extreme as to obliterate the capillaries (Fig. 3, overleaf). The glomeruli in this case showed large amounts of stainable lipid in areas which also stained for amyloid.

Tubular changes were surprisingly slight compared with the glomerular damage. In only three cases was there severe tubular loss and in one of these practically all tubules had disappeared (Fig. 4, overleaf). In biopsies with less severe tubular loss there was either atrophy or disappearance of proximal convoluted tubules related to severely involved glomeruli. Atrophic tubules lined by a flattened type of epithelium and containing rounded eosinophilic casts were frequently found and when these were numerous the appearance was reminiscent of the changes seen in chronic pyelonephritis. In two cases in which frozen sections were prepared, lipid was present in proximal convoluted tubules. The casts gave negative staining reactions for amyloid.

The arterioles and small arteries of all cases showed thickening in which amyloid could be

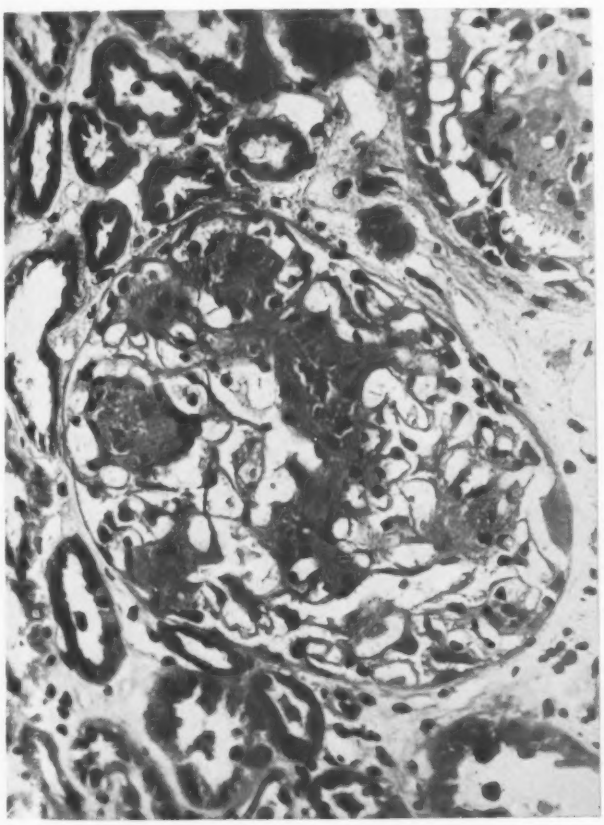

Fig. 1.—Case 6, glomerulus showing early to moderate amyloid change. This takes the form of small "soft" eosinophilic nodules occurring in relation to capillary basement membranes. Haematoxylin and eosin × 240.

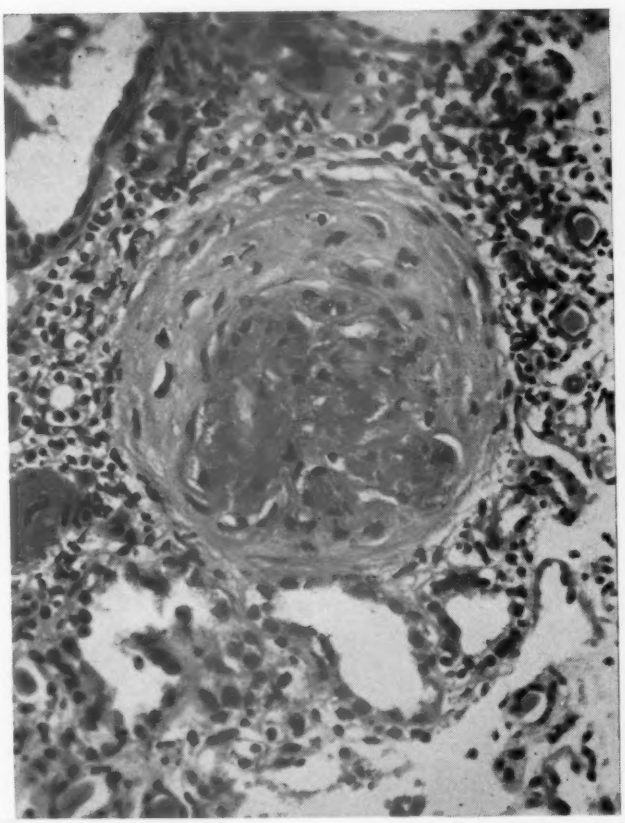

Fig. 2.—Case 4, atrophic glomerulus showing tuft to be structureless and replaced by amyloid with surrounding mantle of collagen. Haematoxylin and eosin × 240.

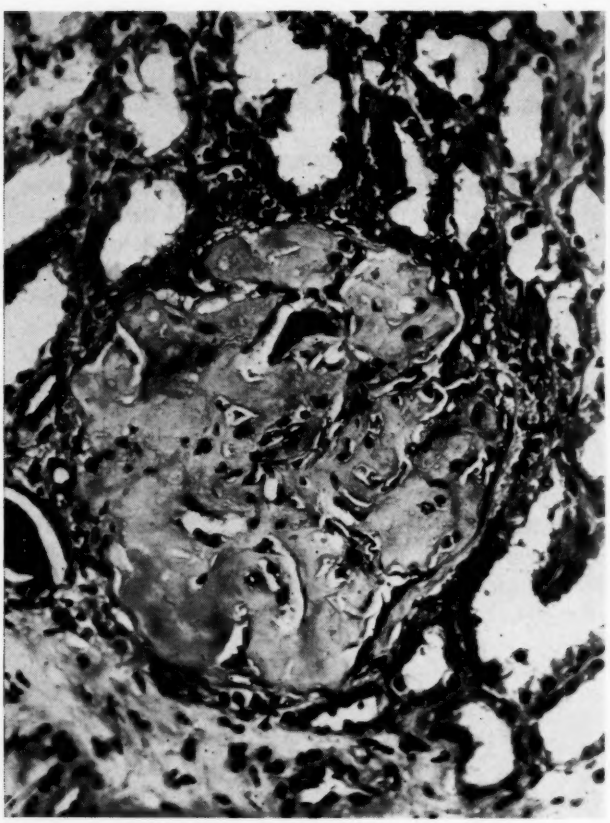

Fig. 3.—Case 9, severe glomerular change in which amyloid is almost completely obliterating the capillaries of the tuft. Haematoxylin and eosin × 240.

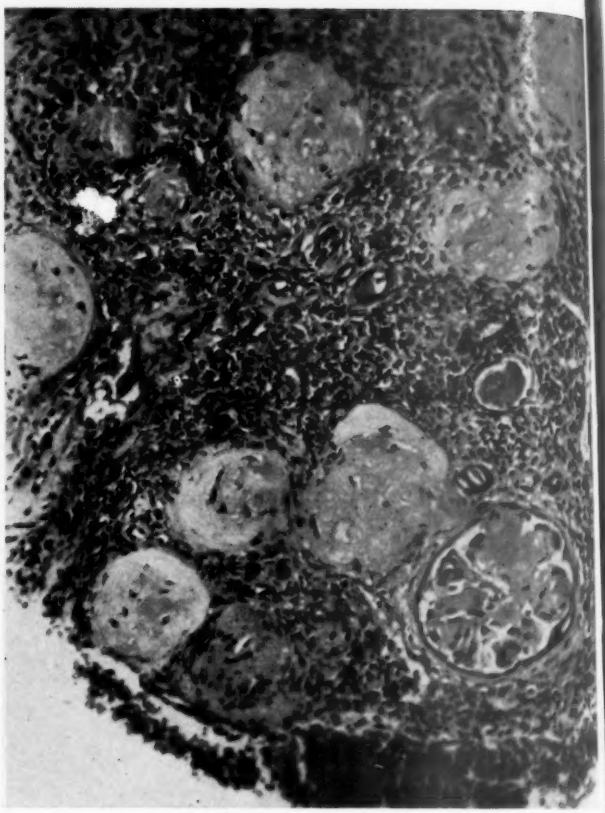

Fig. 4.—Case 7, considerable tubular loss in relation to atrophic glomeruli. Lymphocytes are profuse in the interstitium. Haematoxylin and eosin × 140.

demonstrated. In the least severely involved vessels the amyloid was deposited in the media and adventitial coats. There was no correlation between the amount of amyloid in arteries and the amount in glomeruli. It was slight in the vessels in two cases with extensive glomerular change, and of the two cases with the greatest amount of arterial amyloid one was that with the least severe glomerular change of the whole series. Intimal arterial thickening of either elastic or fibrous type was common.

The interstitial tissue showed increased fibrosis in cases with the most extreme tubular loss, and lymphocytes were often found. In six cases in which the biopsy included medulla, there was amyloid deposition in and around capillary walls and to a lesser extent in tubular basement membranes. The case with the most extensive amyloid in the medulla was one of the two with the most severe vascular amyloid and the one with the least glomerular amyloid of the series.

Discussion

The pathological changes conform to previous descriptions (Bell, 1933), and very little can be added. It is of interest, however, that Case 9 showed extensive deposits of lipid stainable with Oil Red O in those parts of the glomeruli which contained amyloid. Most descriptions of the staining properties of amyloid indicate that there is no lipid content (Wagner, 1957; Braunstein and Buerger, 1959), and although Symmers (1956) referred to abundant finely dispersed sudanophil lipid occurring in some amyloid deposits, the amount in the present case was striking. This particular case was one in which there was no antecedent history of any of the diseases usually associated with amyloid.

Several points of interest were noted in these patients. Hypertension was seen more commonly than has been described in previous series of patients with renal amyloid involvement. Rosenblatt (1933), in 87 cases, never found the systolic blood pressure

over 140 mm. Hg, and Dixon (1934) found systolic blood pressure over 150 mm. Hg in only four out of 35 cases. In patients with renal failure and amyloid infiltration, Mark and Mosenthal (1938) found a raised blood pressure in only three out of twenty cases. Before the use of specific therapy for infections such as tuberculosis and osteomyelitis, the presence of amyloid infiltration is likely to have occurred with persistent infection. The metabolic complications of long-standing infection may prevent the development or maintenance of hypertension, and it is possible that the patients in the present series showed a greater incidence of hypertension which was due to their relatively good general condition.

Amyloid renal involvement is always listed as a cause of the nephrotic syndrome. At the time of renal biopsy all the patients had proteinuria, in some exceeding a loss of 10 g. per 24 hrs. Nevertheless, only four patients had oedema at any time, and in only two was this more than slight. The plasma albumin concentration was not markedly reduced except in Cases 6 and 7, nor was the plasma cholesterol usually raised, exceeding 300 mg./100 ml. in only one patient. In two patients (Cases 1 and 4) proteinuria had been known to be present for 8 and 3 years respectively and yet no oedema had been present.

In one patient (Case 9) there was no history or evidence of any underlying disease and a presumptive diagnosis of primary amyloidosis was made. In the other ten cases there was a history of osteomyelitis in five, of pulmonary tuberculosis in two, of chronic purulent bronchiectasis in two, and of rheumatoid arthritis in one. The association of amyloid infiltration with these conditions has been well documented in the past and is not reviewed here. In both patients with bronchiectasis (Cases 8 and 11), recurrent infection persisted, and in Case 5 the rheumatoid arthritis was active and progressive. In Case 4 there had been no evidence of active tuberculosis for 3 years, and in Case 10 for 10 years; it is, however, not possible to exclude the presence of small caseating foci. In Case 3 active osteomyelitis had been present up to a few months before renal amyloidosis was shown by biopsy. In the other four cases with a past history of osteomyelitis the interval between the last evidence of activity and the proof of the presence of renal amyloidosis by biopsy ranged from 8 to 40 years. In Case 7, however, there was a history of ulcerative colitis during a period of 2 years up to one year before the renal biopsy, and this may have resulted in the renal amyloid infiltration, although evidence from the literature for amyloidosis complicating ulcerative colitis is very sparse. In Case 6 there was no evidence of any infection or necrosis in the wounded knee for 40 years, nor had there been any major illness during this time. Although this patient had been admitted to hospital for minor illnesses on several occasions, proteinuria was not found until some months before the renal biopsy. It is impossible to say whether the old knee wound and the amyloid deposition are causally linked, but long intervals of apparent inactivity of the bone lesion before the finding of renal amyloid are present in other cases. In view of this and of the well-known association between osteomyelitis and amyloidosis, it is difficult to discount the old injury as the cause for the amyloidosis in Case 6. Brouet, Chrétien, and Legrain (1958) described two *post mortem* cases of pulmonary tuberculosis with renal amyloid infiltration in which proteinuria was absent in life, and another similar patient in whom proteinuria was only intermittently present. The apparent absence of proteinuria for long periods after any activity in an underlying lesion in the patients in the present series cannot be taken as evidence against renal amyloid infiltration. It may be possible that once amyloid deposition has started in the kidneys there may be progression, although there is no longer any active underlying lesion. The rate of progression must, however, be slow in these patients and of quite a different order from that in the patient described by Muehrcke, Pirani, Pollak, and Kark (1955), in whom the degree of amyloid infiltration, as judged by repeated renal biopsies, progressed markedly in the space of one year and the urea clearance fell from 46 ml./min. to 2 ml./min.

The most surprising finding in these patients is the good renal function in view of the severe infiltration with amyloid. Histologically extensive glomerular infiltration by amyloid sometimes occurred without any gross abnormalities in the tubules, but in other cases tubular damage was severe (Cases 1, 3, and 7). The dissociation between structural changes and renal function was not confined to those cases with slight tubular involvement. This is most strikingly illustrated by Case 7, in which there were very gross histological changes and yet very good renal function with creatinine clearance repeated on two occasions of the order of 92 ml./min., and a maximum urinary concentration as judged by specific gravity of 1,030. This raises the question of the validity of renal biopsy in reflecting the overall renal changes. Previous descriptions of the distribution of amyloid in the kidney and our own examination of kidneys obtained at autopsy, indicate that the glomerular involvement is diffuse, and it is hard to conceive

that the biopsies reported in this series fail to reflect the true state of affairs in the kidney. In Case 7, in order to minimize the chances of an unrepresentative piece of material, three separate pieces were obtained from the same kidney at the same time. There was no significant difference in the degree of involvement in the three specimens. However, Brouet and others (1958) have described one case where severe involvement with amyloid was found at *post mortem* in one kidney, while the other was normal; pulmonary tuberculosis was present and was accepted as the underlying cause for the amyloidosis. Apart from this case which is difficult to understand we have found no record of localized renal amyloid. The explanation for this divergence between structure and function is unexplained.

In three patients, Cases 7, 10, and 11, a gum biopsy for amyloid was negative, as was the Congo red test in Cases 2, 7, 8, and 10, and in Case 11 a liver biopsy was negative 3 months before the positive renal biopsy at a time when proteinuria was already present. If evidence of renal involvement is present and the possibility of secondary amyloidosis is considered, a renal biopsy would seem to be both the most direct and certain method of making a diagnosis.

Summary

(1) Eleven cases of amyloid disease of the kidney have been encountered in 220 successful percutaneous needle biopsies of the kidney.

(2) In ten cases there was antecedent disease: osteomyelitis in five, pulmonary tuberculosis in two, chronic purulent bronchiectasis in two, and rheumatoid arthritis in one.

(3) A diastolic blood pressure over 100 mm. Hg was found in six cases.

(4) It was striking that the tendency to develop a full nephrotic syndrome was uncommon even with prolonged proteinuria.

(5) A feature of the series was the dissociation between structural change and renal function.

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Amyloïdose rénale

RÉSUMÉ

(1) Au cours de 220 ponctions efficaces du rein, on a trouvé onze cas d'amyloïdose rénale.

(2) Dans dix des cas, il y avait eu une maladie antécédente: ostéomyelite dans 5 cas, tuberculose pulmonaire dans deux, bronchiectasie purulente chronique dans deux, et arthrite rhumatismale dans un.

(3) On a trouvé une tension artérielle minima de 100 mm. de Hg dans six cas.

(4) On a été frappé par le fait que la tendance à développer un syndrome néphrotique classique était rare même dans les cas d'albuminurie prolongée.

(5) Un des traits remarquables de la série était la dissociation entre les altérations structurales et la fonction rénale.

Amiloidosis renal

SUMARIO

(1) Entre 220 punciones biópsicas de riñon llevados a cabo con éxito, se encontraron 11 casos de amiloidosis renal.

(2) En diez de estos casos existía enfermedad previa: osteomielitis en cinco, tuberculosis pulmonar en dos, bronquiectasis con infección purulenta crónica en dos y artritis reumatoide en uno.

(3) En seis enfermos la presión vascular diastólica era de 100 mm. de Hg.

(4) Llamó la atención el hecho de la escasa tendencia que presentan estos enfermos a desarrollar un síndrome nefrótico clásico, aún en casos con prolongada proteinuria.

(5) Resulta remarcable la disociación encontrada entre los cambios estructurales y la función renal.

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FRACTURES IN STILL'S DISEASE

BY

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The introduction of corticosteroid therapy in rheumatoid arthritis was followed by reports of fractures, particularly vertebral, occurring in patients receiving such treatment. This paper reviews the incidence and types of fractures occurring in patients with juvenile rheumatoid arthritis who have attended this hospital during the past 12 years, a small number of whom have received steroid therapy.

Material and Methods

The material consists of 216 cases of juvenile rheumatoid arthritis seen since 1947 and followed to June, 1959. For this diagnosis to be made, a polyarthritis involving four or more joints, commencing before the age of 16 years, and persisting for more than 3 months, without evidence of other disease such as systemic lupus erythematosus, ulcerative colitis or psoriasis, either initially or at follow-up, was required. 26 cases with involvement of less than four joints were also included when a synovial biopsy was compatible with the diagnosis, as were 48 patients with peripheral polyarthritis who later showed radiological sacro-iliac changes without spinal involvement.

A careful study of any earlier hospital records and the original *x* rays is made at the initial assessment of all cases referred here. In-patients are regularly reviewed, and, except under special circumstances, out-patients are seen at least annually, when a full history is taken of events occurring since the previous visit. Any relevant episode reported is investigated by contacting the doctor or hospital where treatment was given.

The basic management of all these cases has consisted of physiotherapy with emphasis on active exercises, hydrotherapy, rest-splints for affected joints, and salicylates. Steroid therapy has been given sparingly and (with the exception of twelve cases treated as part of the Medical Research Council trial of its value in early cases of rheumatoid arthritis) only to patients in whom the disease could not be controlled by simpler measures, when indicated by complications such as iritis, or (in some instances) when it had been given before admission and could not be discontinued. Thus, the majority of patients receiving steroids were those more severely affected by the disease. For the purposes of this analysis the term "maintenance steroid therapy" is restricted to those patients receiving continuous steroid therapy for a minimum period of 3 months; this was so in 63 of the 216 cases, and of these, 43 have received continuous therapy for more than one year. A lateral *x* ray of the spine has been performed on these patients annually whenever possible and when specifically indicated by complaint of pain or loss of height.

Incidence of Fractures

26 of the 216 patients sustained fractures; in four this occurred on two occasions and in two on three occasions, giving an overall incidence of 34 fracture episodes. A single episode of trauma was responsible for multiple fractures, *e.g.* femur and tibia in two cases, so that the femur was involved in nineteen patients, the tibia in six, the humerus, radius, and fibula each in two, and the ulna and metatarsus each in one (a total of 33 long bone fractures), whilst in the remaining seven cases the vertebral column was involved. Fractures of the spine have been counted as single fractures, although in five cases there was involvement of more than one vertebral body (Table I).

TABLE I

INCIDENCE OF FRACTURES IN 216 CASES OF STILL'S DISEASE TO JUNE 1, 1959

Therapy	Total No. of Cases	No. with Fractures	No. of Fracture Episodes	Site	
				Vertebrae	Other Bones
Routine	153	19	25	2*	23
Maintenance Steroid ..	63	9†	9	5	4

* One of these patients had had two months cortisone therapy elsewhere.

† This includes two patients who previously sustained fractures on routine therapy.

Aetiological Factors

Sex and Age at Onset.—Six (6·7 per cent.) of the ninety males and twenty (15·0 per cent.) of the 126 females in the series had fractures. When the cases were further subdivided according to the age at onset, it was found that a high proportion of fractures occurred in girls in whom the disease commenced before the age of 5 years; this difference does not reach statistical significance (Table II).

TABLE II
AGE AND SEX OF CASES STUDIED

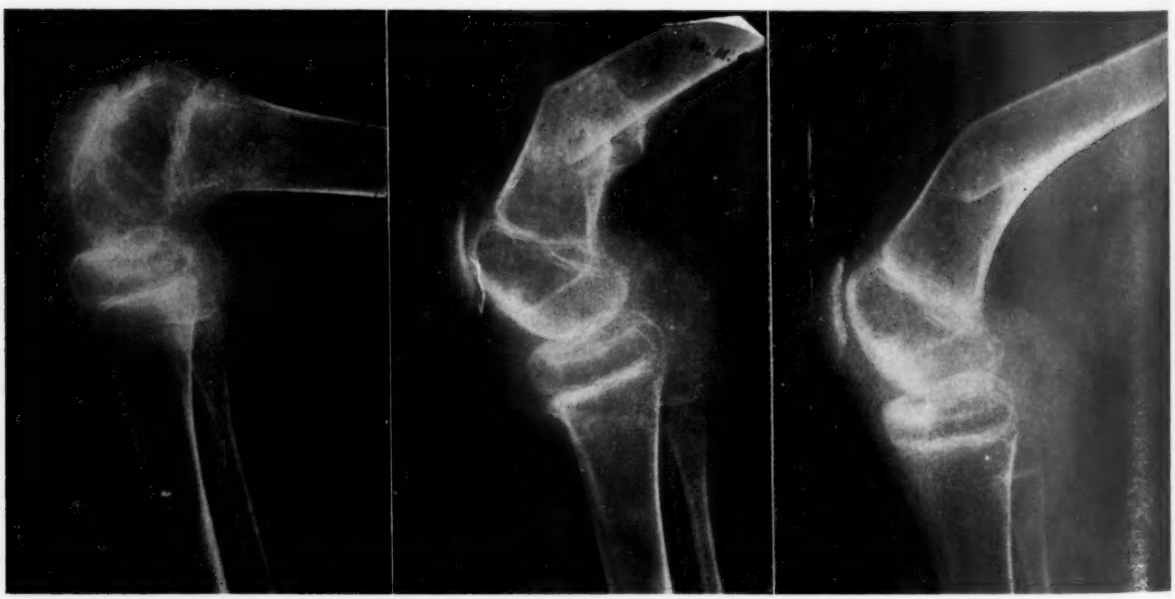
Age at Onset (yrs)	Males		Females	
	Total No. of Cases	No. with Fractures	Total No. of Cases	No. with Fractures
0–5	20	1	50	14
5–10	33	3	31	4
10	37	2	45	2
Total ..	90	6	126	20

Severity of Disease.—All patients were graded according to the severity of the disease process as a whole, and classed as mild, moderate, or severe, and in patients who sustained fractures the presence of disease activity at the time of fracture was noted (Table III). Nineteen of the 26 patients were found to be in the most severely affected group, and in all of these the disease was active at the time of the fracture. The four inactive cases were all leading normal lives at the time of the fracture. In three the fracture was thought to be incidental—for example, a boy who fractured the tibial spine of an unaffected knee while playing rugby football, a girl who fell and sustained a Colles fracture in a wrist which was clinically and radiologically normal, and a girl whose fractured metatarsus was discovered on a routine foot *x* ray. The fourth, however, had recovered from a mono-articular arthritis of the knee with a residual slight flexion deformity when she tripped and fell to the ground fracturing the femur immediately above the affected knee.

TABLE III
FRACTURES RELATED TO SEVERITY OF DISEASE

Severity of Disease Process	Total No. of Cases	Cases Sustaining Fracture		
		Number	Active	Inactive
Group I Mild ..	32	2	—	2
Group II Moderate	99	5	3	2
Group III Severe ..	85	19	19	—

Immobilization.—Impaired movement due to pain and difficulty in using the affected joints is characteristic of rheumatoid arthritis, and when this is further limited by splints or rest in bed rapid osteoporosis results. More than half the patients in the series who subsequently sustained fractures had been confined to bed elsewhere, usually with active arthritis, for a period of at least 3 months during the course of their illness. The period of rest was sometimes much longer when an initial diagnosis of rheumatic fever had been made (Case 1) or when systemic manifestations were marked.



September, 1957 November, 1957 October, 1958

Fig. 1.—Fracture of femur following manipulation with subsequent healing but residual angulation (Case 1).

Trauma.—Twenty fracture episodes followed an episode of trauma; this was of a minor character on fourteen occasions, for example a jolt in a taxi, but in seven cases the trauma occurred in children who had resumed normal activity and was more severe, varying from a skating accident and an injury at rugby football to being run over by a tractor. Three fractures were a direct result of manipulation (Fig. 1, opposite).

In eleven episodes no history of trauma was obtained; seven of these, including five vertebral fractures, occurred in the steroid-treated group.

Role of Maintenance Steroid Therapy.—Four fractures, two of which occurred within 7 days of starting steroid therapy, and another which resulted from a skating accident before the first 3 months of therapy had been completed, as well as the fourth in a girl who had received 2 months' steroid therapy one year before admission, are included in the routine therapy group.

Nine patients on maintenance steroid therapy sustained fractures. Two patients, who had had fractures while on a conservative regime, later developed vertebral collapse while on maintenance steroid therapy, but preceding fracture cannot be used as a contraindication to such therapy as three similar cases have subsequently been maintained on steroid therapy without further incident. The type of therapy included ACTH, cortisone, prednisone, and triamcinolone, the daily maintenance dose varying between 25 and 100 mg. cortisone or its equivalent.

There was no obvious difference in the overall incidence of fractures in the two groups, but there was a significant difference in the site of fracture. Of the nine patients who sustained fractures whilst receiving maintenance steroid therapy, five showed *x*-ray changes of vertebral collapse (Fig. 2, Case 2), the duration of steroid therapy before the initial vertebral fracture being 7, 13, 20, 21, and 32 months respectively. Only two (Fig. 3) of nineteen patients in the other group showed similar changes and one of these had had 2 months of cortisone therapy one year previously.

Fig. 2.—Multiple vertebral fractures in long-standing Still's disease on maintenance steroid therapy (Case 2).

Fig. 3.—Collapse of 8th dorsal vertebra (cf. Fig. 2) in a girl aged 7 who had had Still's disease for 4 years and had never received steroid therapy.

TABLE IV

LESIONS OF THORACIC AND LUMBAR SPINE IN STILL'S DISEASE

Therapy		Maintenance Steroid	Routine
No. with Spinal *X* Rays		Less than 1 year 14 (20) 1 year or more 41 (43) } 63	95 (153)
Lesions	Vertebral Collapse	5	2*
	Adaptive Changes in Vertebrae	1	4
	Other Vertebral Lesions ? Osteochondritis	0	2
	Total	6	8

* This includes the patient who had cortisone therapy for 2 months before admission.

When the incidence of vertebral lesions in the whole series was reviewed (Table IV), slight narrowing of the anterior border of one or more vertebrae without true collapse was seen in some bed-fast cases, and this was thought to be adaptive.

Method of Presentation

Pain was the presenting symptom in all but one of the 25 fracture episodes which occurred in patients not having steroids, but in only five of those who were receiving steroids. The majority of vertebral fractures were discovered in the course of routine spinal *x* rays, although occasionally they were suspected because of pain or apparent loss of height. In only one (Case 2, Fig. 2) was there complaint of severe pain; this occurred with her first crush fracture and in subsequent incidents pain was not a pronounced feature.

Sequelae

No fracture was immediately followed by a generalized flare of activity of the disease, but some local sequelae were noted, such as a recurrent knee effusion following a fractured femur in one girl, tubular resorption of the femur in a boy (Fig. 4),

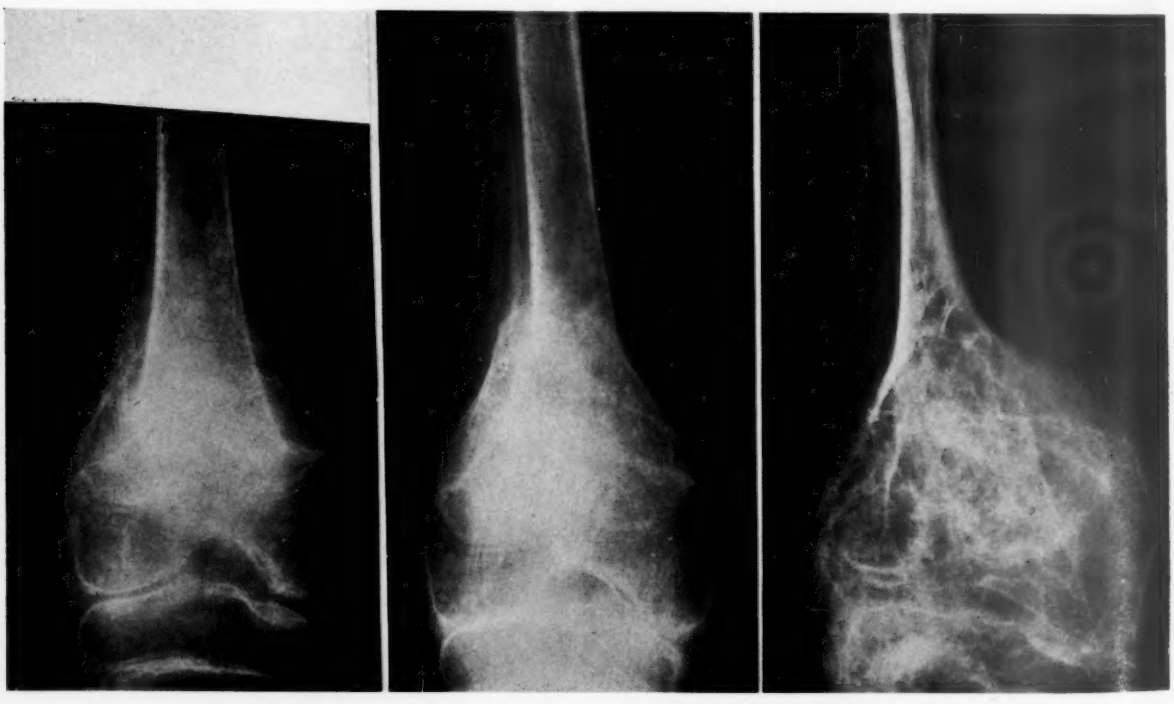


Fig. 4.—Development of tubular resorption of femur, which occurred over 4 years in a boy whose femur had been fractured during manipulation one year after the onset of severe Still's disease at age 9.

There was also persistent angulation and flexion deformity of the femur in two cases (*e.g.* Case 1, Fig. 1), and ankylosis of an elbow following immobilization (Case 3, Fig. 5).

Fig. 5.—Fracture in mid-shaft of humerus after a fall at school, where the severely involved shoulder and elbow became fixed following immobilization (Case 3).

Both prolonged rheumatoid activity and the use of corticosteroids are associated in children with a failure to grow in height (Ansell and Bywaters, 1956), and the additional factor of vertebral collapse may exaggerate this deformity (Case 2, Fig. 2).

Healing of the long bones was not significantly retarded either by the presence of active disease or by steroid therapy in the dosage employed (Case 4, Fig. 6).

Fig. 6.—Healing of fractured femur which was treated with minimal immobilization, maintenance cortisone therapy being continued (Case 4).

Discussion

With the exception of the review of 157 cases of adult rheumatoid arthritis in which fractures occurred in 9·6 per cent. (Den Oudsten and Speyer, 1959), the number of children sustaining fractures in the present series (11·6 per cent.) appears higher than the figures given in previously published results in cases of adult rheumatoid arthritis. Indeed, Good, Vernier, and Smith (1957), when discussing the complications of steroid therapy, commented on the absence of fractures among 75 patients with Still's disease who had not received steroid therapy, while the large group of patients with both rheumatoid arthritis and degenerative joint disease

described by Baer (1941) and the adults with rheumatoid arthritis receiving cortisone therapy reviewed by Boland (1951) have incidences of 1·2 per cent. and 2·6 per cent. respectively.

The high incidence of vertebral fractures in the steroid group in our small series is in agreement with other reports (Table V); of the fourteen patients with rheumatoid arthritis who sustained fractures described by Baer (1941) none of whom had received steroids, only one episode involved the vertebral column, whereas in the steroid-treated cases described by Boland (1951), Demartini, Grokoest, and Ragan (1952), and Curtiss, Clark, and Herndon (1954) vertebral fractures were more common, and Good and others (1957) comment on the occurrence of vertebral fractures in two patients with Still's disease who had received steroids.

When Cushing (1932) originally described the syndrome resulting from hypersecretion of the adrenal cortex, he commented on the marked osteoporosis of the skeleton and particularly of the spine. This observation has been confirmed in subsequent reports, such as that of Howland, Pugh, and Sprague (1958) who showed that of 69 patients whose radiological changes were reviewed, 68 showed osteoporosis affecting mainly the spine, pelvis, and ribs, with vertebral fractures in 42 per cent. usually involving the lower thoracic or upper lumbar spine. From the pathological viewpoint, Follis (1951) found rarefaction of the trabeculae with adequate numbers of osteoblasts and no evidence of osteoclastic resorption in the ribs and vertebra of four adults who had died from this disorder. Similar effects on retardation of chondrogenesis and osteogenesis have been reported after the use of ACTH in experimental animals (Baker and Ingle, 1948), and negative calcium balances are well recorded in association with corticosteroid therapy (Sprague, Power, Mason, Albert, Mathieson, Hench, Kendall, Slocum, and Polley, 1950).

The high overall incidence of fractures in this series has led to a review of the management of our cases. As both active disease and immobilization lead to osteoporosis (Ropes, Rossmeisl, and Bauer, 1943; Deitrick, Whedon, and Shorr, 1958), particularly in those children with disease commencing before the age of 5 years, immobilization, either general or local, should be employed for the shortest possible period. Rest in bed in the very acute stage and when indicated by severe or painful hip disease should be accompanied by daily active exercises, assisted if necessary at the outset, and adequate analgesics should be given to allow this active participation, while hydrotherapy should be employed whenever it is available. Even when weight-bearing is allowed, the necessity for active exercises under supervision is still present. Once improvement is well under way, the patient should be encouraged to lead as normal a life as possible, but full physical activity should not be advised until the disease is completely quiescent, as minor injury can cause a fracture while osteoporosis persists. The need for continued daily exercises at home during this period is stressed at each out-patient visit.

The use of rest-splints from the onset will prevent the majority of deformities, but if these do occur manipulation of a joint should not be undertaken until adequate serial splinting has failed to improve its position.

The indications for corticosteroid therapy should

TABLE V

FRACTURES IN ARTHRITIS

Date	Author	No. of Cases	Type of Disease	Steroid Therapy	Patients Sustaining Fractures		
					Number	Vertebrae	Other Bones
1941	Baer	1,625	Chronic Arthritis (Degenerative Joint Disease + Rheumatoid Arthritis)	−	21 (14 with Rheumatoid Arthritis)	1	13
1957	Good and others	75	Juvenile Rheumatoid Arthritis	−	—	—	—
1959	Den Oudsten and Speyer	143 14	Rheumatoid Arthritis Rheumatoid Arthritis	− +	15 (9·6 per cent.)	4	11
1951	Boland	76	Rheumatoid Arthritis	+	2	1	1
1952	Demartini and others	?	Rheumatoid Arthritis	+	5	5	1
1954	Curtiss and others	?	Rheumatoid Arthritis (1 juvenile)	+	4	4	—
1955	Bunim, Ziff, and McEwen	8	Juvenile Rheumatoid Arthritis	+	—	—	—
1957	Good and Others	?	Juvenile Rheumatoid Arthritis	+	2	1	1

be carefully weighed against the very real risk of multiple vertebral fractures, which are particularly likely to occur when osteoporosis is already present. Thus, preliminary assessment of each case includes a lateral *x* ray of the thoracic and lumbar spine. As steroid therapy is frequently associated with marked weight increase, some restriction of diet is often required and when this is ordered in children it is wise to bear in mind that the intake of bread and milk, both good sources of calcium, is frequently reduced, so that if this restriction continues for any length of time calcium supplements are desirable. The value of anabolic steroid in preventing calcium loss due to corticosteroid is not known. Short-term studies have shown that calcium retention can be induced with the concurrent use of Nilevar in moderately high dosage (Stokes, Horwith, Pennington, and Clarkson, 1959), but whether it is possible to cover maintenance steroid therapy without running into side-effects from the anabolic steroid is still not certain.

Despite all these measures, fractures do occur, and when this happens they require special management with the shortest possible period of immobilization, together with intensive physiotherapy and rapid rehabilitation (Case 4, Fig. 6).

Summary

(1) In a series of 216 cases of juvenile rheumatoid arthritis, 26 patients sustained fractures, six on more than one occasion; five of the seven spinal fractures involved multiple vertebrae.

(2) There appeared to be a higher incidence of fractures in female patients in whom the disease commenced before the age of 5 years.

(3) 63 patients received maintenance steroid therapy and although the total incidence of fractures was not significantly different in those given steroids from that in those not given steroids, the incidence of vertebral collapse among those on steroid therapy was significantly higher.

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Fractures dans la maladie de Still

RÉSUMÉ

(1) Dans une série de 216 cas d'arthrite rhumatismale juvénile, 26 cas subirent diverses fractures, six d'entre eux plus d'une fois. Dans cinq cas sur sept de fracture de la colonne vertébrale, plusieurs vertèbres furent atteintes.

(2) La proportion des fractures semblait être plus grande chez des filles dont la maladie avait commencé avant l'âge de cinq ans.

(3) Dans cette série, 63 cas furent soumis à une thérapie de maintien par des stéroïdes et, bien que le nombre total de fractures chez ceux-ci ne fût pas appréciablement différent par rapport aux autres, la fréquence de l'affaissement vertébral chez eux fut appréciablement plus grande.

Fracturas en la enfermedad de Still

SUMARIO

(1) Entre una serie de 216 casos de artritis reumatoide juvenil, 26 sufrieron fracturas diversas, seis de ellos en más de una ocasión. En cinco de las siete fracturas de columna vertebral encontradas, habían sido afectadas varias vértebras.

(2) La mayor incidencia de fracturas aparece entre enfermas cuyo padecimiento comenzó antes de los cinco años de edad.

(3) Sesenta y tres casos de esta serie estuvieron sometidos a una terapéutica de mantenimiento con esteroides y, aunque no se encontró ninguna diferencia significativa en cuanto al número total de fracturas en éstos en relación con los demás, la incidencia del aplastamiento vertebral fué significativamente mayor dentro del grupo que recibió tratamiento con esteroides.

APPENDIX

Case Reports

Case 1. A girl when aged 6 commenced with polyarthritis and constitutional symptoms in April, 1956, and was admitted to this hospital in August, 1957, with severe involvement and deformity of elbows, wrists, hands, hips, knees, and ankles. As only limited progress was made on salicylate and physiotherapy, her hips and knees were manipulated and she was started on steroid therapy.

Routine *x* rays taken after manipulation confirmed a supracondylar fracture of one femur with angulation; this was treated with splinting and gradual remobilization (Fig. 1).

Prednisone (10 mg./day) caused a steady improvement in her clinical state but attempts to reduce the dosage caused marked deterioration, so she continued at this dose. After 21 months she was noted to have lost half an inch in height, and an *x* ray revealed collapse of the 7th dorsal vertebra.

Case 2. A girl aged 14 months in 1948 developed arthralgia, fever, rash, nodules, and lymphadenopathy which lasted for 6 months. She then remained well until the age of 4 years when she was re-admitted to hospital complaining of abdominal pain. Laparotomy was unhelpful, her pyrexia persisted, and she subsequently developed pericarditis and arthritis. Steroid therapy for 2 months caused a marked improvement which was maintained until the relapse for which she was admitted to this hospital in February, 1952.

She was then found to have polyarthritis, a typical rash, lymphadenopathy, hepatosplenomegaly, fever, anaemia, and generalized osteoporosis. Shortly after admission she was given suppressive cortisone therapy (100-62·5 mg./day for one year, then 37·5 mg./day). She was discharged after 19 months in hospital and followed as an out-patient when repeated attempts were made to reduce her steroid dosage.

After 32 months of continuous therapy she was re-admitted in November, 1954, complaining of pain in the back, and an *x* ray of the dorsal spine showed a compression fracture of D.8. Steroid dosage was lowered, although her clinical condition deteriorated, and was finally stopped in March, 1955, after a haematemesis requiring blood transfusion. An attack of measles in June, 1955, was followed by remission, and she was discharged, but during the next year her condition steadily deteriorated until in July, 1956, she was bed-fast with widespread active arthritis and was almost moribund. After many painful interviews with the mother, steroid therapy was reluctantly restarted and during the next 2 years, whilst on hydrocortisone and later triamcinolone, further fractures, the majority painless, were found in seven other dorsal and lumbar vertebrae (Fig. 2). In addition she has developed pseudoxanthoma elasticum, and a clinical diagnosis of amyloidosis was confirmed in 1958.

Case 3. A girl aged 2½ years developed pain and swelling of the small joints of the hands and feet, followed by pain in the hips, knees, and elbows. A diagnosis of rheumatic fever was made elsewhere and she was kept in bed for 6 months by which time the joints had fully recovered. When she was aged 5, joint pains recurred and she was again treated as a case of rheumatic fever for a further 6 months at the same hospital.

For the next 2 years she remained generally unwell and when re-admitted at the age of 7 years a diagnosis of Still's disease was made and she was treated with gold injections and immobilization.

From that time until admitted here at the age of 11 she was unable to walk. After 8 months of intensive physiotherapy she was mobilized on walking sticks and able to get about freely. One year later while at school she fell and fractured the mid-shaft of the humerus (Fig. 5). This was treated locally by immobilization in plaster, but after removal of the plaster both the elbow and shoulder were fixed and she has subsequently required an arthroplasty of the elbow.

Case 4. A girl aged 8 was admitted to hospital in 1952 with fever, polyarthritis, and pericarditis. During the next 3 years, three further relapses were treated with cortisone.

When she was admitted to this hospital at the age of 11 years there was widespread joint involvement which improved on salicylates and intensive physiotherapy. A subtrochanteric abduction osteotomy was performed in 1956 for adduction deformity of the left hip. Physiotherapy was continued whilst she was in bed and she recommenced walking with support 2 months later.

6 months after the operation a further acute exacerbation was treated with steroids and she has since been on maintenance therapy (cortisone 50 mg./day). She remained well and mobile until in 1959 at the age of 15 years, she fell downstairs and sustained a transverse fracture of the left femur 2 inches above the knee. She was admitted to our orthopaedic unit and the leg was put in a Thomas's splint for 4 weeks. During this period she continued on maintenance steroids and had daily physiotherapy. She was then mobilized in the hydrotherapy pool for 4 weeks. After a further 4 weeks she was able to walk without a caliper and 3 weeks later she was discharged. At that time the affected hip and knee on the fractured side showed exactly the same mobility as before the fracture (Fig. 6).

Ann. rheum. Dis. (1960), **19**, 143.

HAEMOPHILIA AND HAEMOPHILIC ARTHROPATHY*

AN HISTORICAL REVIEW AND A CLINICAL STUDY OF 42 CASES

BY

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Haemophilia in man is uncommon, with a prevalence of about 2-3 per 100,000 in Great Britain, but even so, this means there are about 1,500 haemophiliacs in this country. In Northern Europe and North America cases are frequently found, whilst fewer have been reported in the Latin countries (Biggs and Macfarlane, 1957, 1958). In Australia, the incidence is somewhat higher (de Gruchy, 1958). In Asiatics and Negroes of pure breeding, the disease seems to be almost unknown (Nesbitt and Richmond, 1949; Pachman, 1937), cases which have been described almost all having some European ancestry. The only animal in which a similar condition has so far been found is the dog (Hutt, Rickard, and Field, 1948; Graham, Buckwalter, Hartley, and Brinkhous, 1949).

It seems probable that about half those born haemophilic reach adult life and develop joint manifestations, but concentrated preparations of anti-haemophilic globulins (AHG), which are likely to be more widely available in the future, may enable more to live longer. It may be of interest to look at the present problem of joint disease and deformity, and at the methods which aim at preventing it, relating by the way a little of the history of this disease and its arthropathy.

I. HISTORICAL ASPECTS

The word "haemophilia" was introduced into medicine by Hopff (1828), a pupil of J. L. Schönlein, but there are many references in older literature to diseases which could have been haemophilia. In the Babylonian version of the Talmud (a commentary on Jewish life, written in the 5th century A.D.) the story is told of four sisters who lived in Zipporah in the 2nd century A.D.; the first of them had her child circumcized, and he died; likewise the second and third sisters with their first-born sons; when the fourth sister brought her child along, the Rabbi, Simon ben Gamaliel, ordered that she should not have him circumcized, lest the same fate should befall him (Tractate Yebamoth, fol. 64). A second Talmudic reference (Tractate Shabbath, fol. 134a) describes the experience of the Rabbi Nathan, who, on a visit to a far country, was accosted by a woman "who had circumcized her first son and he had died and her second son and he had died: the third she brought before me. Seeing that he was red, I said to her, wait until his blood is absorbed. So she waited until his blood was absorbed and circumcized him, and he lived . . . On another occasion (a similar history) seeing that he was green I said to her, wait until he is full blooded; she waited and circumcized him, and he lived."

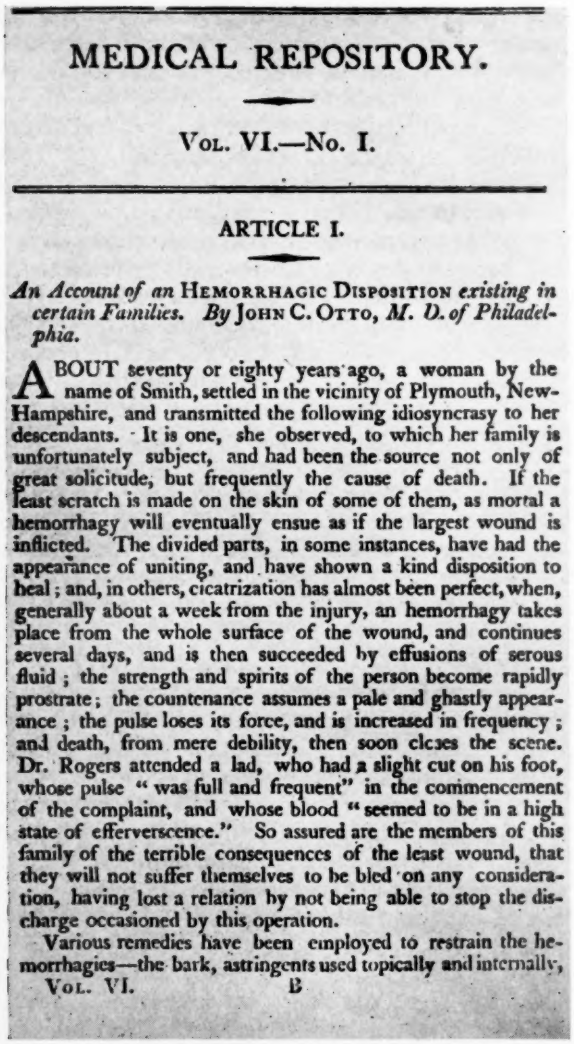
These two rather confusing stories were interpreted by Katzenelson (1884), who considered that in both instances haemophilia was the disease concerned, for he felt it unlikely that two brothers would have died after circumcision otherwise. In the Hebrew, the word "red" had the connotation of "reddish-black", and he considered this to mean that the child showed bruises following a difficult delivery, for as he pointed out, a reddish colour is normal in the skin. "Green", he felt, like the later word "chlorosis", meant the pallor of a severe anaemia, perhaps related to umbilical or internal haemorrhage. It is interesting that in each case, later circumcision did not prove fatal, and that the children were each named after the Rabbi whose advice had been taken!

In the 11th century, Khalif Ibn Abbas, commonly called Albucasis (quoted by Sköld, 1944), described a village where the males suffered from a disease manifested by uncontrollable bleeding from wounds and mucous membranes. In the 14th century,

* Paper read at a meeting of the Heberden Society on December 4, 1959.

a Jewish man was reported to have lost two sons after circumcision, but when his third arrived, this time by a second wife, circumcision was performed without incident. There were a number of similar histories of possible haemophiliacs.

The first reliable account of the disease was given by Dr. John Otto of Philadelphia, who was in his late twenties at that time (Otto, 1803). In between tending victims of a widespread yellow fever epidemic, he prepared for publication (Fig. 1) observations of the descendants of a woman named Smith, who had settled in Plymouth, New Hampshire, and had transmitted to her children a tendency to bleed excessively from wounds. He noted that males only were affected, and that the trait was transmitted through the females of the line. Otto also mentioned in his paper a Dr. Benjamin Rush, who told him of other cases, one in York, and another in Northampton county, U.S.A., and a Mr. Boardley, who told him of a family in Maryland. It would thus appear that the disease was fairly well known in New England, early in the 19th century.



MEDICAL REPOSITORY.

VOL. VI.—No. I.

ARTICLE I.

An Account of an HEMORRHAGIC DISPOSITION *existing in certain Families. By* JOHN C. OTTO, *M. D. of Philadelphia.*

ABOUT seventy or eighty years ago, a woman by the name of Smith, settled in the vicinity of Plymouth, New-Hampshire, and transmitted the following idiosyncrasy to her descendants. It is one, she observed, to which her family is unfortunately subject, and had been the source not only of great solicitude, but frequently the cause of death. If the least scratch is made on the skin of some of them, as mortal a hemorrhagy will eventually ensue as if the largest wound is inflicted. The divided parts, in some instances, have had the appearance of uniting, and have shown a kind disposition to heal; and, in others, cicatrization has almost been perfect, when, generally about a week from the injury, an hemorrhagy takes place from the whole surface of the wound, and continues several days, and is then succeeded by effusions of serous fluid; the strength and spirits of the person become rapidly prostrate; the countenance assumes a pale and ghastly appearance; the pulse loses its force, and is increased in frequency; and death, from mere debility, then soon closes the scene. Dr. Rogers attended a lad, who had a slight cut on his foot, whose pulse "was full and frequent" in the commencement of the complaint, and whose blood "seemed to be in a high state of efferverscence." So assured are the members of this family of the terrible consequences of the least wound, that they will not suffer themselves to be bled on any consideration, having lost a relation by not being able to stop the discharge occasioned by this operation.

Various remedies have been employed to restrain the hemorrhagies—the bark, astringents used topically and internally,

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Fig. 1.—First page of Dr. J. Otto's article (1803).

By 1813 there was quite an extensive literature on bleeding diseases, mainly in the United States and Germany. Dr. John Hay of Reading, Mass., which at that time was a small town near Boston, described in that year the pedigree of the Appleton-Swains, descendants of Oliver Appleton (Hay, 1813). Felt (1834), in his *History of Ipswich, Essex, and Hamilton*, cited this family as one of the curiosities of the district. In his writings, Hay described the disease quite fully, and with much practical experience, as some members of the affected family were his next door neighbours. He appeared quite perturbed about the whole problem, and it was not until the last paragraph of his paper that the reason became apparent:

> "My eldest son, Jonathan P. Hay, married a descendant of Mr. Appleton, and has eight children by her: three sons, the youngest about eight years and has the exact complexion of the bleeders, but has not as yet bled more than common. I am apprehensive that he will exhibit the haemorrhagic disposition."

Subsequent records of the Appleton family (Osler, 1885; Pratt, 1908) do not support Hay's apprehension.

Blagden (1817), Surgeon Extraordinary to the Duke of Kent, published the first reliable English report of the disease. His patient had, as a child, bled for 3 weeks after a dental extraction and had later had a cut on his forehead which bled excessively. The final episode, at the age of 26, was haemorrhage following dental extraction, which continued even after his carotid artery had been ligated.

Bulloch and Fildes (1912) published a comprehensive review of haemophilia with over 900 references, in which early cases of excessive bleeding are fully analysed.

HAEMOPHILIC ARTHROPATHY

The first record of excessive bleeding associated with arthritis, was that of Philip Hoechstetter, of Augsburg, who in 1674 described a case that could well be one of haemophilia. This was of a boy who bled profusely, first at birth from the umbilical cord, and whilst a youth from the nose and subcutaneously, who was also recorded as having haemorrhages into the joints, though details are not given.

A

TREATISE ON HÆMOPHILIA

SOMETIMES CALLED THE

HEREDITARY HÆMORRHAGIC DIATHESIS

BY

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Omnia membra
Emisere simul rutilatum sanguine virus:
Sanguis erant lacrimae: quaecumque foramina novit
Humor, ab his largus manat cruor: ora redundant
Et patulae nares: sudor rubet: omnia plenis
Membra fluunt venis: totum est pro vulnere corpus.
LUCANI *Pharsalia.*

LONDON
H. K. LEWIS 136 GOWER STREET
M DCCC LXXII

Fig. 2.—Frontispiece of Dr. J. Wickham Legg's monograph (1872).

Early references to haemophilic arthropathy are much less numerous than those of exterior bleeding. Little was written about joint manifestations before the end of the 19th century, and most of that came from France and Germany. In the 1860s, Volkmann (quoted by Vegas, 1914) noted that haemophilia and scurvy might be localized in the joints. More recently, Volkmann's ischaemic contracture has been described in haemophilia following haemorrhage into the muscles of the forearm (Groves, 1907; Lord, 1926; Hill and Brooks, 1936; Thomas, 1936; etc.).

J. Wickham Legg, of St. Bartholomew's Hospital, in 1872 wrote a monograph (Fig. 2) in which he described five cases personally seen, with excessive bleeding from minor wounds and after dental extractions, and with spontaneous and easy bruising. Three of these had joint troubles: the first had swelling of the knees intermittently for 6 years before he was seen; the second had pains in the knees, but no swelling; the third had intermittent swelling of the knee from age 4, and by the time he was seen at age 13 it was "out of its natural shape, and caused him to walk lame". The knee

was greatly enlarged on its inner aspect as if the bone ends themselves were enlarged, and the joint seemed to contain fluid. Pain was a feature in all three cases and other joints, hips and ankles, were involved, but not to the same extent.

The best early description of haemophilic arthropathy came from Germany, where König (1892) published a thorough study of eight cases. In two of his cases he operated on the joint, and both patients died of haemorrhage 3 and 10 days later.

Evolution of Treatment

Early methods of treatment of haemophilia are of some interest. Otto, and later Hay, both suggested that a purging dose of sodium sulphate, daily for 3 or 4 days, would stop the bleeding, or, if it did not, to quote the words of both of them "a more frequent repetition is certain to do so". Later authors suggested various procedures, including special diets, purging, and even venesection. Vegas (1914) used subcutaneous injection of rabbit serum with some success. In truth, nothing done was of real value until comparatively recently with the use of fresh blood transfusions at times in massive quantities, and latterly with the use of AHG to stop the bleeding.

Advances in Diagnosis

Modern methods of diagnosis have shown that a number of factors concerned in the clotting mechanism may be deficient, but in patients with a suggestive clinical picture over 80 per cent. of cases are true haemophiliacs. Christmas disease, the commonest of the other forms of haemophilia, was first described in the U.S.A. by Aggeler, White, Glendening, Page, Leake, and Bates (1952) as "plasma thromboplastin component" deficiency. The name came from that of the first sufferer investigated in Britain, in a joint report from Oxford, Capetown, Plymouth, and the Postgraduate Medical School by Biggs, Douglas, Macfarlane, Dacie, Pitney, Merskey, and O'Brien (1952). Other and rarer types of clotting deficiency have since been recognized. Anti-haemophilic globulin is a labile component of the plasma globulin, and is consumed in the clotting process. Its administration appears to be of greatest value because thereby is supplied the lacking component necessary for clotting in true haemophilia. Because of the lability of AHG, it is essential that blood used for transfusion should be fresh. AHGs have been prepared both from human and animal (beef and pig) plasma, but the large amount of plasma necessary is only one of the difficulties that makes the cost of these very high. The animal types have the added disadvantage of becoming less effective after about 10 days' administration (Macfarlane, Mallam, Witts, Bidwell, Biggs, Fraenkel, Honey, and Taylor, 1957). Christmas factor is much more stable than AHG and stored blood may be suitable for transfusion, although it seems best to give fresh blood (Brafield and Case, 1956).

Famous Sufferers from Haemophilia

In England, haemophilia has been of special interest because of the involvement of the descendants of Queen Victoria (Haldane, 1938; Sköld, 1944; Iltis, 1948). Her son Leopold was a haemophiliac, and the gene was transmitted through two of her daughters, Alice and Beatrice. Among the former's descendants was Czarina Alexandra of Russia, and among the latter's Queen Eugenia of Spain, both of whom had haemophiliac sons. Various researches have been made into the House of Saxe-Coburg-Gotha, from which both Queen Victoria and Prince Albert were descended, but no definite earlier case has been found. It thus seems most likely that a genetic mutation occurred in Victoria or her parents.

Probably the most widely known haemophiliac was Czarevitch Alexi, heir-apparent to the throne in Russia at the time of the Revolution, who was a great-grandson of Queen Victoria. Fear for his health dominated the life of his mother, Alexandra, and provided the basis for the influence of the "monk" Rasputin, who claimed to be able to stop the bleeding, and who could in fact comfort Alexi even by speaking to him on the telephone (Buchanan, 1954). An American, Cumston (1918), reported on "good authority" that the boy had distension of the knee joints and discolouration of the ligaments, resulting in difficulty in walking, as a legacy of haemophilic haemarthroses. A member of the Czar's household, a sailor, was accustomed to carry Alexi around when he was having trouble (Buchanan 1954). Alexi, a puny boy, twice nearly died of haemorrhage before perishing in the Revolution in 1918.

II. CLINICAL STUDY

In the present study a systematic examination was made of the joints of patients who had been referred to the Department of Haematology at the Postgraduate Medical School of London for a suspected bleeding diathesis and who were proved to have one of the forms of haemophilia. The 42 cases in this series were those seen personally out of 77 known haemophiliacs living in London and the Home Counties, to whom letters were sent asking them to attend for an examination. Failed follow-up cases

included three who had died, six not traced, fifteen who were traced but did not reply, and eleven who, for various reasons, were unable to come. All cases seen were given a full medical examination. *X* rays were taken of the involved joints, as well as routine films of the hands, feet, and knees, and in the first 25 seen, of the cervical spine.

Clinical Findings

Of the 42 cases seen, 39 were suffering from true haemophilia (Haemophilia "A"), whilst three had Christmas disease (Haemophilia "B"). Ages ranged from 5 to 69 years and all were males. Only 24 gave a positive family history, which is in accord with most recent series, though proportions vary widely in many (Biggs and Macfarlane, 1958).

In 83 per cent. of cases, the first symptom occurred in the early years of life—haemorrhage after circumcision in the neo-natal period (14 per cent.), prolonged bleeding from a comparatively minor wound under the age of 5 (45 per cent.), and bruising (18 per cent.) being most common. Three cases had curious modes of presentation, one aged 67 with melaena, another aged 44 with post-operative haemorrhage after incision of a perianal abscess, and the third aged 46 with bruising and bleeding after scalene node biopsy. All of these patients had haemophilia of mild degree.

Three patients only presented with their first episodes in a joint; one had a haemarthrosis in the ankle at the age of 18 months, whilst the other two had knees involved when aged 5.

Case 1, a man born in 1932, was admitted to hospital in 1938 with pain and swelling of the right knee, diagnosed as tuberculosis and treated with rest and splinting. Some months later, however, a dental extraction was followed by persistent bleeding, and haemophilia was diagnosed. Subsequently he has had about twelve recurrences of haemarthrosis in both knees, and he now has a little residual deformity. His previous history revealed only an episode of somewhat excessive bleeding from a comparatively minor wound on the foot. An elder brother has subsequently been found to be a haemophiliac.

Of our 42 cases (Table I), fourteen gave no history of episodes involving the joints; of the 28 with such a history, 23 showed abnormal signs of joint involvement on physical examination.

TABLE I

FREQUENCY OF JOINT INVOLVEMENT IN HAEMOPHILIA

History of episodes involving the joints	28
Residual signs of joint involvement	23
No history or signs of joint involvement	14
Total	42

The knee was the joint most commonly involved (Table II), 25 out of 28 patients with joint manifestations having had the knees affected. Ankles, elbows, and hips were the next most frequent. Most patients had both signs and symptoms of joint disease in each affected joint, but some, as might be expected, had symptoms only in one or more joints. In five cases, however, there were signs of involvement (*e.g.* loss of full range of movement and *x*-ray changes) in joints about which no history of any joint trouble whatever was obtainable. In all these five patients, other joints were involved both on history and on examination.

TABLE II

PATTERN OF JOINT INVOLVEMENT IN 28 PATIENTS

Joint	Total No. of Patients	Symptoms and Signs	Symptoms Only	Signs Only
Knees	25	20	5	—
Elbows	22	19	3	—
Ankles	22	14	8	—
Hips	19	11	5	3
Wrists	13	7	5	1
Shoulders ..	10	4	6	—
Fingers	9	4	4	1
Toes	6	2	4	—
Jaw	3	—	3	—
Spine	—	—	—	—

Those who had had numerous episodes of haemarthrosis often found it impossible to remember just how often various joints had in fact been involved. With haemarthroses occurring every month or so, joint pains seem to have become part of their everyday life. One patient, aged 22, made an interesting observation—he had noticed that the pain was more severe when swelling was marked and bruising was not, but that it was less severe and less prolonged when the bruise "came out".

Of the true haemophiliacs, the 24 who first presented after the middle of 1955 have had their plasma AHG level estimated quantitatively by members of the staff of the haematology department. The sixteen patients with a low AHG level (below 2 per cent.) have a high incidence of joint involvement, only one not having had haemarthroses, and twelve having residual signs (Table III); of eight

TABLE III

RELATION OF AHG LEVEL, FAMILY HISTORY, AND JOINT EPISODES IN 24 HAEMOPHILIACS

No. of Cases	AHG (per cent.)	Family History		Acute Joint Episodes		Residual Joint Changes	
		+	−	+	−	+	−
16	2 or Less	9	7	15	1	12	4
8	Over 2	6	2	1	7	1	7

with a AHG level over 2 per cent., only one has had haemarthroses, and he has minimal deformities. A positive family history did not show any relationship with AHG level (Table III).

Management of Acute Haemarthroses

Few acute haemarthroses were seen. The joints, whilst acutely painful, should be rested or splinted in the position of optimal function—thus no pillows should be allowed under the knees, nor should an extreme degree of flexion of the hip be permitted. If the AHG level can be raised by blood or plasma transfusion to that necessary for effective haemostasis, and if the patient is seen early in his course, it is reasonable to aspirate the joint, to relieve pressure and pain. As soon as the pain subsides, physiotherapy and gentle muscle setting exercises should be begun—this will probably be on the second or third day—and early weight-bearing should be the aim. It does seem that early emptying of the joint, cessation of bleeding and early restoration of movement are the greatest factors in maintaining normal function in the long run.

Chronic Joint Changes

Examination of chronically affected joints revealed many interesting changes. It was common to find apparent enlargement of the bone ends, loss of normal range of movement, wasting of muscles acting on the joint in question, and often bizarre deformity. In the knee, the femoral condyles were more prominent than usual, with loss of the final 5°-30° of full extension and backward displacement and often rotation of the tibia. In the elbow too, the articulating bones were enlarged, whilst movements were reduced, especially extension. Deformities in the small joints of the hands were not common, and those seen were minimal.

Radiology

In the knees, many different findings were noted. In severe cases, there was narrowing of the joint space, due to cartilage erosion and loss, and frequently irregularity of the joint surface. An appearance of "squaring off" of the tibial and femoral surfaces was found in many cases and osteophytic lipping was common, though not severe. Severe radiological and clinical changes were not always allied with loss of function as in the following cases:

Case 2, a man aged 30, a telephonist, first bled when aged 3 months after circumcision. He has had numerous episodes involving the joints, "hundreds" in all, but mainly in the right knee and the elbows. The right knee (Fig. 3) was found to have 30° flexion and 30° valgus deformity and marked posterior subluxation of the tibia. The range of movement is 30°-80°. Despite this the patient is able to walk quite well with a stick, can drive a motor car, and has a sedentary occupation from which he rarely loses time.

Fig. 3.—Case 2, right knee. Note loss of joint space, irregular articular surface, and appearance suggesting collapse of lateral tibial condyle. Note large nutrient artery (Middlemiss, 1960).

Case 3, a man aged 56, a clerk, was first noticed to bruise excessively in the first year of life. He has had "hundreds" of joint episodes involving all the joints of the body, including the temporo-mandibular joint and the small joints of the fingers and toes, but excluding those of the spine. Over recent years he has had fewer haemarthroses and these tend to be of a minor nature. He was found to have a 60° flexion deformity with a range of movement of 60°-85° on the right, and a 30° flexion deformity with range 30°-35° on the left (Fig. 4, opposite).

Despite this he travels to work each day by bus and walks approximately half a mile at each end of his journey. He has not seen a doctor for years.

Osteoporosis was very common in affected knee joints, though a far from universal finding. Gross loss of normal trabecular pattern and coarsening of the remaining trabeculae often gave a cystic appearance in the bone ends. Such changes were not always present, however, and severe residua were at times unaccompanied by osteoporosis or by evidence of past healed porosis, as illustrated in Fig. 5 (opposite, Case 4).

Osteoporosis appeared to have caused collapse of the lateral tibial condyle in some cases, and we feel this, rather than differential lower femoral epi-

Fig. 4.—Case 3, *x* ray of knees, showing gross narrowing of joint space, irregularity of joint surface, and lipping, with a suggestion of "squaring" of the bone ends. Poor detail on the right is due to a 60° flexion deformity of the knee.

Fig. 5.—Case 4, a linesman aged 25, who had many episodes of haemarthrosis in the right knee, but none in the left. Note 10° flexion deformity on the right; the film shows squaring, narrowing of joint space, and lipping, but no obvious osteoporosis.

physeal overgrowth, to be responsible for such valgus deformities at the knees as were seen in Case 2 above (Fig. 3).

Overgrowth of epiphysis was seen in the distal end of the femur, but only in two juvenile cases, one aged 14 and the other aged 8, and in neither was there any greater increase in one condyle than in the other. In none of the adults was the result of such a differential growth change seen.

Overgrowth of the patella (Escande and Tapie, 1919) is well illustrated in Case 5, a boy aged 8 (Fig. 6, overleaf), in whom there is an increase on the left side, in which he had had eight or ten haemorrhages, when compared with the unaffected right side.

"Squaring" of the lower end of the patella, as stressed by Jordan (1958), was seen in only four of the 25 patients with affected knees. All of these had had their first episodes before puberty, and thus before growth was completed. Irregular calcification of cartilage was seen in the line of growth of the lower femoral epiphysis as it advanced into the articular cartilage in Case 5. Such irregularity can be seen in normal subjects, especially by magnification techniques, but it is of lesser degree (Bywaters, 1959).

Fig. 6.—Case 5, a boy aged 8, had numerous haemarthroses in the left knee, but none in the right. Note increase in size of left patella when compared with the right, and the irregular line of advancing calcification in the femoral condyle on the left when compared with that on the right.

Growth arrest lines, common in normal subjects and in Still's disease, were seen frequently, and were in four instances unusually prominent (as noted by Middlemiss, 1960):

Case 6, a boy aged 12, first bled after circumcision when 8 days old. Since the first joint episode in the right wrist in 1948, he had had many haemarthroses, involving all the large joints of the body, plus those of the hands and feet. In June, 1958, he developed a haematoma in the lower thigh, which became spontaneously infected, despite surgical drainage the infection spread to involve the bone. In the sequestrum (Fig. 7) the growth arrest lines are especially prominent. The patient, now aged 12, has a chronic discharging sinus, the pus from which is only rarely blood-stained.

Fig. 7.—Case 6, a boy aged 12, with chronic osteomyelitis of femur following an infected haematoma. Note growth arrest lines in sequestrum.

Haemosiderosis of the joint capsule (Alexander and Landwehr, 1948; Doub and Davidson, 1926; Newcomer, 1939; MacDonald and Lozner, 1943; Collins, 1951) was not seen in the *x* rays of any of our cases, though it has been seen in previous cases at this hospital (Bywaters, 1959).

In twelve of the eighteen patients in whom the elbows were *x*-rayed, there was enlargement of the head of the radius in the affected joint. This is well seen in Cases 7 and 8. Case 7 (Fig. 8) had had numerous episodes in the right elbow but none in the left, and Case 8 (Fig. 9, overleaf) had had six haemarthroses on the right side and none on the left.

Other changes seen commonly in the elbow joints were loss of joint space and lipping, the latter usually of comparatively minor degree.

In the ankles, flattening of the upper articular surface of the talus was seen in advanced cases, along with marked lipping. The lower end of the tibia was at times enlarged, as seen in the ankle of Case 9, a man who had had many episodes in this joint (Fig. 10, overleaf). Case 10, a young man aged 19, had an ankylosed talo-tibial joint (Fig. 11, overleaf), but this was the only ankylosed joint, either fibrous or bony, found in our whole series of 155 affected joints. Erosion of the joint surfaces was found quite frequently in the ankles.

In the hands, osteoporosis was seen commonly, even when there was neither history nor signs of local joint involvement. Two curious changes were seen. Fig. 12 (overleaf) shows the carpus of Case 11, a man aged 49, who has no history of joint episodes nor of any injury to the wrist and in whom, on clinical examination, the wrist joints are perfectly normal. Such cystic changes have been found in two other cases with similar negative histories and with clinically normal wrists.

Cases 12 and 13 (aged 21 and 14), the former without a history of episodes in the right wrist but with some limitation of movement and the latter without

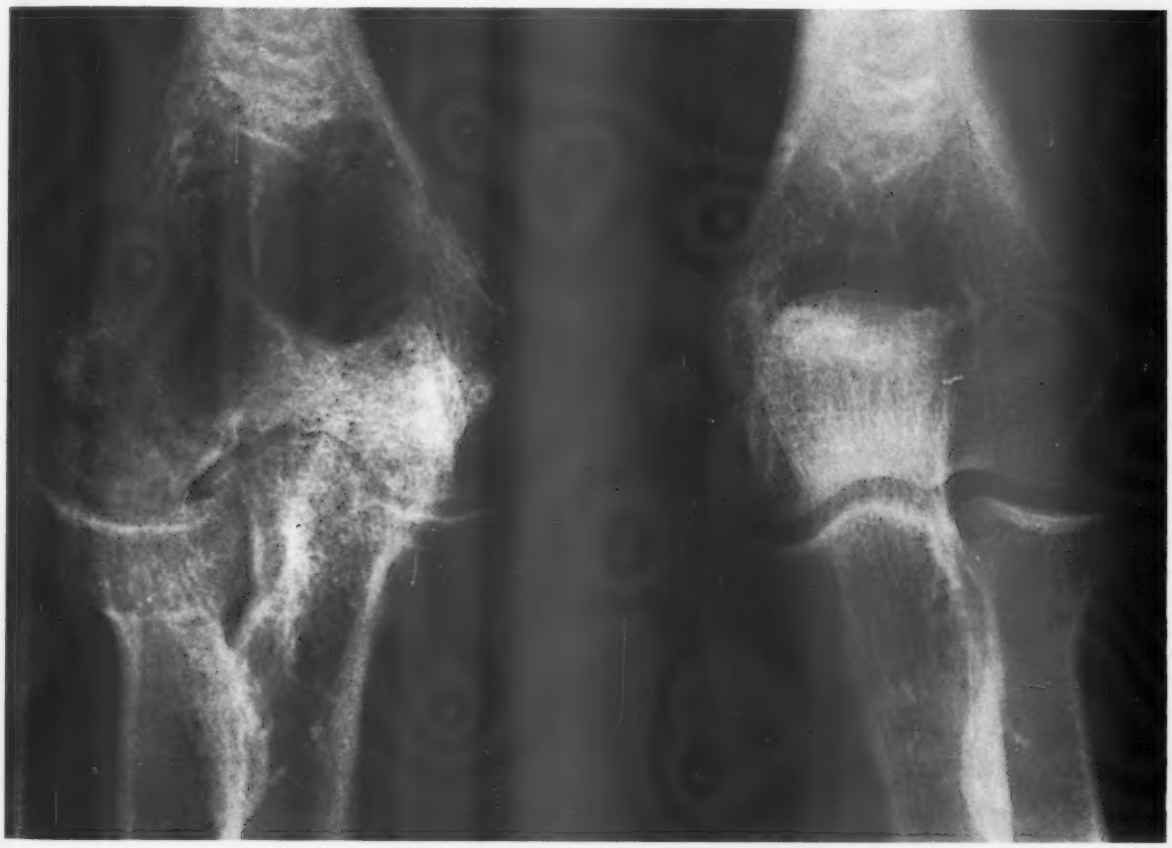

Fig. 8.—Case 7, a man aged 44, had severe haemophiliac arthropathy, but the left elbow and left hip were never involved. The right elbow has a 45° flexion deformity and can only be bent to a right-angle; pronation and supination are half normal. The left elbow normal. Note narrowing of joint space on the right and marked enlargement of the right radial head.

Fig. 9.—Case 8, a man aged 25, had six haemarthroses in the right elbow but none in the left. Note enlargement of right radial head.

any wrist involvement, showed a curious radiographic picture at the distal end of one ulna (Fig. 13A, B, overleaf). Such changes are probably due to disturbance of epiphyseal growth by haemorrhage involving the epiphysis. Records of a similar change in a haemophiliac have not been found, though Newcomer (1939) described, without illustration, a case in which at the left wrist "the ulna is shortened; it does not articulate with the wrist".

No haemophilic pseudo-tumours (Firor and Woodhall, 1936; Ghormley and Clegg, 1948) were seen in the series.

An interesting change was seen in the hip of Case 14, a 25-year-old haemophiliac, an intelligent man who was certain that he had had no trouble in his hip joint (Fig. 14, overleaf). Examination revealed marked loss of rotation and abduction. In contrast to this painless involvement, recurrent painful haemorrhages into a joint which showed no residual changes have been seen from time to time, as in the case of a man aged 22 with Christmas disease, who had had recurrent episodes of bleeding into all the major joints without clinical or radiological change.

Clinical Pathology

The erythrocyte sedimentation rate (Westergren) was tested in 31 cases and was below 10 mm./hr in 29; in two with histories of recent upper respiratory tract infections, however, it was above 40 mm./hr. The differential agglutination test (D.A.T.) was performed (Table IV) to see if repeated episodes of inflammatory joint involvement could lead to the presence of the rheumatoid factor in the blood. The test was positive in only one patient, a boy aged 14 with Christmas disease, who showed a titre of 1 : 256. There was no family history nor clinical evidence of rheumatoid arthritis. His latex fixation test was also positive, as was that of one other man aged 44 with severe joint deformities.

TABLE IV
SEROLOGICAL TESTS IN 32 CASES OF HAEMOPHILIA

Test	No. of Patients Tested	Result	
		Positive	Negative
Differential Agglutination ..	32	1 (1 : 256)	31
Latex Fixation	28	2	26

Fig. 10.—Case 9, a solicitor aged 41, had many haemarthroses in the left ankle as a child, usually following minor sprains. Note widening of lower end of tibia in its AP diameter, loss of joint space, sclerosis in articulating bones, and cystic appearance in lower end of tibia.

Schooling and Occupation

Those with more than minor degrees of joint involvement in childhood all had difficulty in attending school. Most missed at least 2 years, but subjectively all felt they were able to keep up with their class fellows when able to attend. In view of likely disability in later life, it is most desirable that such patients be admitted to hospitals where schooling facilities on the wards are available. Of the six boys in our series in the school age range, three are attending ordinary schools (though two of these, who have haemarthroses, miss a great deal), whilst two of the other three can only potter about at home and one is in an institution for chronic illnesses.

Only five out of the 35 adults are unable to work. 22 have sedentary jobs, mostly clerical, but eight are doing various kinds of manual work. Case 15, a man aged 34, with no evidence of joint disease is a prison warder. He practises judo in his spare time but plans to give this up as his wife objects to the frequent bruises. His AHG level is 7·5 per cent.

Discussion

Most previous writers on haemophilic arthropathy have reported small numbers of cases personally seen (Klason, 1921; Key, 1932; Buus, 1935), though larger series of haemophiliacs, some of whom had arthropathy, have been recorded. Thomas (1936) described 98 haemophiliacs, of whom 77 gave a history of joint symptoms and sixty had permanent deformities. Birch (1937) described 98 patients, of whom 83 gave a history of joint symptoms and 66 had residual deformities. Davidson, Epstein, Miller, and Taylor (1949), on the other hand, noted that 38 out of forty cases had chronic joint changes, though their series was not apparently selected because of arthropathy. More recently, Rodnan, Lewis, Warren, and Brower (1957) have fully investigated 53 bleeders (44 with true haemophilia and nine with Christmas disease), of whom 47 had had haemarthroses and 42 had objective changes in the joints. Jordan (1958) has dealt exhaustively in an excellent monograph with over 100 cases of haemophilic arthropathy, many of whom were

Fig. 11 —Case 10, a man aged 19, with severe generalized haemophiliac arthropathy. Note plantar flexion deformity of foot due to ischaemic contracture in calf muscles, flattening of upper articular surface of talus, and bony ankylosis of ankle joint.

Fig. 12.—Case 11, a clerk aged 49, with no history of haemarthroses, nor of any bone or joint injury to the hands or wrists, which are clinically normal. Note "cysts" in carpus.

treated by orthopaedic measures to improve function.

The low follow-up rate, in which only 42 of the 77 haemophiliacs sought were seen, is of interest. A few of our patients, usually the older ones, were very loath to attend hospital, stating that the little that was done for them in hospital while they were young had been of more harm than value. These people now avoid hospitals whenever they can, and such an attitude among others may have accounted for some of the cases which were not followed up. Others were unwilling to take time off work to attend, because they normally lost too much time when their disease was "active".

Some patients with recurrent joint episodes found that the same joint or group of joints was always involved. Thus one patient had many episodes in the right knee and elbow and none elsewhere, whilst another had one ankle and both elbows involved repeatedly but no other haemarthroses.

The pathogenesis of chronic joint changes is not known. Repeated haemarthroses, *e.g.* in patients with haemangiomata, do not produce such joint changes as are seen in haemophilia, nor were similar changes produced experimentally by Key (1929) who injected the joints of dogs repeatedly with citrated blood. It seems to us, as to Key (1932) and to Rodnan and others (1957), that subchondral and intra-osseous haemorrhage in the bone ends, either primary or as an extension from a haemarthrosis in an already damaged joint, may cause ischaemic lesions of articulating bone, with secondary osteoarthrosis—a sequence similar to that of Caisson disease.

Fig. 13(A).—Case 12, a man aged 21, has no history of episodes in the right wrist, but movement is slightly diminished (60°—0°—60°) in comparison with that in the left wrist (75°—0°—75°).

Fig. 13(B).—Case 13, a boy aged 14, has no history or signs of wrist disease.
Both show obliquity of the ulnar epiphyses in the right wrist and widening of the lower ulnar shaft.

Fig. 14.—Case 14, a civil servant aged 25, had no history of haemarthroses in the hips, though other joints had been affected. Note flattening and shortening of femoral head, with cystic appearance underlying cartilage. The joint space is well preserved.

If such is the case, the best way to prevent irreversible damage would be to stop the bleeding and decompress the joint—moreover, this should be viewed as a medical emergency.

Enlargement of the radial head would seem to be the most characteristic and possibly diagnostic feature of haemophilic arthropathy. Similar changes have been described, but only rarely (De Palma and Cotler, 1956; Middlemiss, 1960). It is interesting to note that the original description and radiological demonstration of this change was given by Shaw from Bristol in 1897, only 2 years after Roentgen reported the discovery of *x* rays. Enlargement of the radial head is seen in one of the radiographs reproduced by Buus (1935), though the author does not comment upon it. Our findings of minimal changes in the hands conflict with those of Hart (1955), who considers that haemarthroses in such joints are especially liable to result in destructive changes.

Summary

The historical aspects of haemophilia and haemophilic arthropathy are reviewed.

In 42 cases of haemophilia, 28 gave a history of haemarthroses, whilst 23 had permanent joint deformities of varying grades of severity. In one case, joint disease had been initially attributed to tuberculosis.

In this series, an anti-haemophilic globulin level of 2 per cent. or below was associated with joint manifestations in fifteen, and with residual joint deformity in twelve, of sixteen cases; when the level was above 2 per cent., joint manifestations and minimal residual deformity were seen in only one of eight cases.

Recurrent haemarthroses may be associated with clinically and radiologically normal joints whilst, conversely, changes may be found in joints in which the patient can give no history of past episodes.

The most characteristic radiological change of haemophilic arthropathy was an enlargement of the head of the radius, which was seen in two-thirds of those with involved elbows. Some patients with severe residua of multiple episodes of haemarthrosis

were able to lead quite normal lives despite their deformities.

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DISCUSSION

DR. J. SHARP (*Manchester*): I should like to ask about the cause of pathological cystic changes in the wrists.

PROF. E. G. L. BYWATERS (*London*): I should like to make a comment on the changes seen and described as causing ulcerative lesions opposite each other, usually in the knee. It seems to me that this might be a type of osteochondritis dissecans, due to trauma, with bleeding separating out the bit of bone-cartilage at that particular area of the joint, but we have no evidence for this. I wonder whether anyone has seen this before and has pathological data on the process?

DR. J. J. R. DUTHIE (*Edinburgh*): Why should blood in a joint lead to destructive arthritis?

PROF. S. J. HARTFALL (*Leeds*): I should like to congratulate the speaker on a fascinating review of this subject, well presented.

DR. DUDLEY HART (*London*): Were there any spinal complications of any sort?

DR. J. BALL (*Manchester*): From the work of Prof. Collins one would imagine that haemophilia was not associated with a true arthritis. In the single haemophilic joint I have examined, there had been repeated bleeding into the joint, but there was no synovial hypertrophy or inflammation. Whatever the mechanism of the bony changes it may not be closely related to haemarthrosis. I was struck by the resemblance of the picture of the hip to osteochondritis dissecans; perhaps the changes here are related to haemorrhage beneath the articular cartilage in childhood.

DR. J. FORESTIER (*Aix-les-Bains*): I noticed in the wrists and head of the femur, what looks like an osteonecrosis. Is this a usual mechanism of the joint involvement in haemophilia?

PROF. J. H. KELLGREN (*Manchester*): After the haemarthrosis has subsided and after the blood has been removed, there might not be any sign of inflammation. From a study many years ago, there was no doubt that blood produced a brisk cellular reaction during the period of absorption of the blood into the joint, leaving haemosiderin behind. There is also a systemic reaction due to absorption of blood. You see this with bleeding anywhere in the body. One would have to examine the tissues at the time of the bleeding or shortly after it, when blood is being absorbed, to see this.

DR. DIXON: In answer to Dr. Sharp's question about the cause of cystic changes in the wrists, we do not know, we can only make the observation. In reply to Dr. Duthie's question why a large effusion of blood should cause destructive arthritis, again we do not know. We

assume as many people do, that blood may cause tension inside the bone end and the process may be a question of alteration of the nutrition of the subchondral bone. There may be a vicious circle mechanism, once the bony cortex has been breached further bleeding will cause much more damage by seeping under the cartilage.

We did not see any spinal involvement, only the normal age changes in the older cases.

In reply to Dr. Ball, by inflammatory episodes, we mean the presence of clinical inflammation, with limitation of movement, swelling, heat, and tenderness. We did not see redness.

PROF. E. G. L. BYWATERS (*London*): When we examined joints from a patient with haemochromatosis, we saw a good deal of iron pigmentation in the synovial membrane, but the cartilage was clear. It was in fact a normal joint; but these haemophiliac joints do not look normal at all. There must be some inflammation resulting from the repeated stretching and the effusions which occur, quite apart from the deposition of the iron pigments in the membrane.

Hémophilie et arthropathie hémophilique

RÉSUMÉ

On passe en revue l'histoire de l'hémophilie et de l'arthropathie hémophilique.

Sur 42 cas d'hémophilie, 28 présentèrent des antécédents personnels d'hémarthrose et 23 d'entre eux eurent des difformités articulaires permanentes plus ou moins sévères. Dans un cas la maladie articulaire avait été attribuée initialement à la tuberculose.

Dans cette série, un taux de globuline anti-hémophilique de 2 pour cent ou moins fut associé à des manifestations articulaires dans 15 cas et à une difformité articulaire résiduelle dans 12 cas sur 16; lorsque ce taux fut au dessus de 2 pour cent, des manifestations articulaires et des difformités residuelles minimes ne furent observées que dans 8 cas.

Des épisodes récurrents d'hémarthrose peuvent s'associer à des articulations cliniquement et radiologiquement normales et d'autre part il peut y avoir des altérations pathologiques dans des articulations sans antécédents d'hémarthrose.

L'altération radiologique la plus caractéristique de l'arthropathie hémophilique fut une augmentation de la tête du radius; cette altération fut présente dans deux tiers des cas où le coude se trouvait affecté. Certains malades ayant des séquelles graves après des multiples épisodes d'hémarthrose furent capable de mener une vie normale malgré leurs difformités.

Hemofilia y artropatía hemofílica

SUMARIO

Se revisa la historia de la hemofilia y artropatía hemofílica.

Entre 42 casos de hemofilia, 28 presentaron historia de hemartrosis, en 23 de los cuales existieron deformidades articulares definitivas de grado variable. En un caso la enfermedad articular había sido atribuida inicialmente a tuberculosis.

En 15 casos con presencia de manifestaciones articulares y en 12 entre 16 casos de deformidad articular residual el nivel de globulina antihemofílica era del 2 por ciento o inferior, mientras que en los enfermos con un nivel de hemoglobulina antihemofílica superior al 2 por ciento, manifestaciones articulares y deformidades residuales mínimas aparecieron solamente en uno de cada ocho casos.

Episodios recurrentes de hemartrosis pueden asociarse con articulaciones clínica y radiológicamente normales, mientras que, por el contrario, pueden aparecer cambios patológicos en articulaciones sin historia de episodio anterior.

La alteración radiológica más característica de la artropatía hemofílica encontrada fué un agrandamiento de la cabeza del radio, alteración presente en dos tercios de los casos en los que estaba afectada la articulación del codo. Algunos enfermos con acusadas alteraciones articulares, consecutivas a múltiples episodios de hemartrosis, eran capaces de llevar una vida bastante normal a pesar de sus deformidades.

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ARTHRITIS AND RHEUMATISM IN THE INSURED POPULATION OF NORTHERN IRELAND

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It is impossible to exaggerate the importance of the effect of the rheumatic diseases on the health and economy of the community. For many years those concerned with assessing the health of the nation have relied mainly on the Registrar General's mortality records in the absence of any reliable routine morbidity data. It is clear that, for the relatively non-fatal rheumatic diseases, such data give an inadequate measurement of the invalidism and human suffering involved.

It is not surprising that the problem of rheumatism in industry with its considerable loss of manpower should have attracted most attention and there is in fact little precise information available regarding the incidence in the general population.

The Department of Health for Scotland (1932-37) in pre-war studies reported that about 3 per cent. of the insured population were incapacitated annually because of "arthritis and rheumatism". The difference in the size and structure of the insured population since 1948 invalidates this source for purposes of comparison. Newman (1924) and others have reported that an almost similar percentage of the population consults the family doctors each year with rheumatic complaints which were found to be responsible for one-sixth of the total invalidism of the population. More recently Slater (1946) and Logan and Brooke (1957) have dealt with the records of the Survey of Sickness (1943-52). They indicate a monthly incidence of rheumatism in the general population of just under 20 per cent. This figure will include minor rheumatic conditions not severe enough to cause incapacity for work, and these statistics have the disadvantage of self-diagnosis. Logan and Cushion (1958) have discussed a valuable contribution to morbidity records—a joint study by the College of General Practitioners and the General Register Office. It was found that rheumatic disorders took second place in the list of conditions necessitating consultation in general practice (64·9 per thousand population).

In the industrial field valuable studies have been reported by Lawrence and Aitken-Swan (1952), Kellgren and Lawrence (1952), and Lawrence (1955). Field studies were designed to compare the incidence of rheumatism in miners with that in the general population. From their records it is demonstrated that rheumatic complaints are of frequent occurrence in the general population, and that in miners the incidence of these conditions is no greater than in the population as a whole. The degree of incapacity, however, is greater in miners in terms of loss of working time, and there is evidence of an earlier onset as shown by a higher incidence in the fourth decade.

In spite of advances in recent years in our understanding of chronic rheumatic diseases, the lack of diagnostic definition and the difficulty in precise clinical diagnosis, except in advanced and typical cases, has hampered progress. For this and other reasons it is obvious that morbidity statistics have limitations in comparison with the results of specially-designed field studies and their chief value is to give a broad picture of the problem involved. Here it should be noted that in the diagnostic list the following clinical entities are included in the group "arthritis and rheumatism": acute arthritis—pyogenic and non-pyogenic, rheumatoid arthritis and allied conditions, osteoarthritis and allied conditions, other specified and unspecified forms of arthritis, muscular rheumatism, and rheumatism unspecified.

It is proposed to make some general observations using records of sickness statistics. In this connexion, Stuart-Harris (1954) has shown that it is possible to use the analyses derived from National Insurance data as a basis for estimating the size of

such a problem, in his case bronchitis. Digests of Statistics analysing certificates of incapacity are issued annually by the Ministry of Pensions and National Insurance and show, under fifty main diagnostic headings, the causes of incapacity for work for virtually the entire working population of Great Britain including both employed and self-employed persons. This information is based on doctors' certificates issued for purposes of sickness benefit.

Separate and similar analyses are carried out in Northern Ireland by the Ministry of Labour and National Insurance with a much smaller population at risk. Using this data, Park and Kidd (1958), in a general study on morbidity in the insured population of Northern Ireland, have shown that in terms of the duration of spells of incapacity chronic rheumatism takes a high place and has a longer median duration than that experienced in Scotland. Kidd and Park (1959) have recently shown that this group of diseases makes a very substantial contribution to the long-term sickness problem in Northern Ireland.

Information is available on a 20 per cent. sample basis for four complete years (ending May 31, 1955, 1956, 1957, and 1958 respectively) in the form of new spells commencing each year, the duration of spells completed each year, and the number of spells lasting more than one year. The diagnoses are coded according to the fifty causes of the International Statistical Classification of Diseases.

It is appreciated that here there is diagnostic imprecision in that a group of diseases is covered by the diagnostic heading arthritis and rheumatism. However, bearing in mind this and other limitations of morbidity studies derived from National Insurance sources, it is felt that it is worth while to record statistical data relating to this clinical group.

Table I shows that the inception rates for this group are higher for men and married women than for other women. Although in men and other women the rates are relatively low in the under-30 age group, this is not the case with married women. The inception rates increase with age in men and other women up to age 40 and then become stable. In married women there is evidence that the rates are always higher but continue to increase with age. The rates for males aged 60 to 64 years and for married women aged 50 to 59 years show a marked fall in the course of the four years under review, but there is no evidence of a similar trend among the other women aged 50-59 years.

TABLE I

NUMBER OF NEW SPELLS AND INCEPTION RATES FOR ARTHRITIS AND RHEUMATISM
NUMBER OF SPELLS OF SICKNESS PER 1,000 EXPOSED TO RISK, BY AGE GROUP AND SEX
(20 PER CENT. SAMPLE)

Sex and Marital Status	Age Group (yrs)	1954/55		1955/56		1956/57		1957/58	
		Spells	Inception Rates	Spells	Inception Rates	Spells	Inception Rates	Spells	Inception Rates
Men	15–19	61	8·6	71	10·0	66	9·2	54	7·3
	20–29	233	16·8	288	20·7	275	19·8	240	17·1
	30–39	403	27·6	456	31·2	420	28·6	424	28·6
	40–49	544	37·0	600	40·9	604	40·8	553	37·9
	50–59	456	36·5	528	42·2	498	39·8	491	38·4
	60–64	208	45·2	187	40·7	180	37·5	167	34·0
	Total ..	1,905	28·3	2,130	31·6	2,043	30·1	1,929	28·2
Married Women	15–19	5	—	10	—	6	—	9	—
	20–29	83	33·2	104	41·6	80	28·6	94	34·8
	30–39	49	25·8	61	32·1	68	40·0	61	33·9
	40–49	76	38·0	82	41·0	114	60·0	114	60·0
	50–59	82	58·6	75	53·6	66	47·1	67	44·7
	60–64								
	Total ..	295	36·9	332	41·5	334	41·8	345	42·6
Other Women	15–19	72	9·9	108	14·8	94	12·7	86	11·6
	20–29	91	12·0	124	16·3	104	13·9	112	15·8
	30–39	47	15·7	54	18·0	52	17·3	53	18·3
	40–49	57	21·9	79	30·4	69	26·5	46	19·2
	50–59	69	24·6	78	27·9	70	25·0	87	30·0
	60–64								
	Total ..	336	14·4	443	19·0	389	16·7	384	16·9

The sex-marital ratios of inception rates given in Table II show that the overall rate for other women is about half that for men and less than half that for married women, although the variations with age are appreciable. The overall rate for married women is about one and one half times greater than that for men, but it is double the rate for men between the ages of 20 and 29 years.

Table III, giving the duration of completed spells for arthritis and rheumatism, by sex, shows that in men and in other women only about 40 per cent. of spells last less than 3 weeks against 33 per cent. for married women, and the proportion lasting more than one year is significantly greater for both married and other women than for men in those earlier years but is similar for 1957/58.

TABLE II

RATIOS OF INCEPTION RATES FOR ARTHRITIS AND RHEUMATISM FOR THE THREE SEX-MARITAL GROUPS, BY AGE GROUP

Age Group (yrs)	1954/55			1955/56			1956/57			1957/58		
	Married Women / Men	Other Women / Men	Married Women / Other Women	Married Women / Men	Other Women / Men	Married Women / Other Women	Married Women / Men	Other Women / Men	Married Women / Other Women	Married Women / Men	Other Women / Men	Married Women / Other Women
15–19	—	1·2	—	—	1·5	—	—	1·4	—	—	1·6	—
20–29	2·0	0·7	2·8	2·0	0·8	2·6	1·4	0·7	2·1	2·0	0·9	2·2
30–39	0·9	0·6	1·6	1·0	0·6	1·8	1·4	0·6	2·3	1·2	0·6	1·9
40–49	1·0	0·6	1·7	1·0	0·7	1·3	1·5	0·6	2·3	1·6	0·5	3·1
50–59	1·6	0·5	2·4	1·3	0·7	1·9	1·2	0·6	1·9	1·2	0·8	1·5
All Ages	1·3	0·5	2·6	1·3	0·6	2·2	1·4	0·6	2·5	1·5	0·6	2·5

TABLE III

DURATION OF COMPLETED SPELLS FOR ARTHRITIS AND RHEUMATISM, BY SEX (20 PER CENT. SAMPLE)

Sex and Marital Status	Duration (days)	1954/55 Spells	1954/55 Percentage of Total	1954/55 Cumulative Percentage	1955/56 Spells	1955/56 Percentage of Total	1955/56 Cumulative Percentage	1956/57 Spells	1956/57 Percentage of Total	1956/57 Cumulative Percentage	1957/58 Spells	1957/58 Percentage of Total	1957/58 Cumulative Percentage
Men	1–3	15	0·8	0·8	15	0·7	0·7	11	0·5	0·5	23	1·2	1·2
	4–6	127	6·7	7·5	146	7·1	7·8	170	7·9	8·4	189	9·5	10·7
	7–12	324	17·1	24·6	335	16·2	24·0	368	17·1	25·5	349	17·6	28·3
	13–18	311	16·5	41·1	321	15·5	39·5	332	15·4	40·9	311	15·7	44·0
	19–24	245	13·0	54·1	255	12·3	51·8	269	12·5	53·4	242	12·2	56·2
	25–48	446	23·6	77·7	529	25·6	77·4	570	26·4	79·8	504	25·4	81·6
	49–78	177	9·4	87·1	225	10·9	88·3	171	7·9	87·7	153	7·7	89·3
	79–156	134	7·1	94·2	144	6·9	95·2	138	6·4	94·1	108	5·4	94·7
	157–312	55	2·9	97·1	51	2·5	97·7	56	2·6	96·7	43	2·2	96·9
	312+	56	2·9	100·0	48	2·3	100·0	71	3·3	100·0	61	3·1	100·0
	Total ..	1,890	100·0		2,069	100·0		2,156	100·0		1,983	100·0	
Married Women	1–3	1	0·3	0·3	1	0·3	0·3	1	0·3	0·3	6	1·7	1·7
	4–6	15	5·1	5·4	16	4·9	5·2	16	4·2	4·5	23	6·5	8·2
	7–12	40	13·7	19·1	45	13·8	19·0	56	14·9	19·4	49	13·8	22·0
	13–18	37	12·7	31·8	37	11·3	30·3	61	16·2	35·6	50	14·0	36·0
	19–24	34	11·7	43·5	39	11·9	42·2	49	13·0	48·6	38	10·7	46·7
	25–48	66	22·6	66·1	59	18·1	60·3	77	20·4	69·0	102	28·6	75·3
	49–78	36	12·3	78·4	43	13·1	73·4	40	10·6	79·6	28	7·9	83·2
	79–156	33	11·3	89·7	50	15·3	88·7	30	8·0	87·6	35	9·8	93·0
	157–312	13	4·5	94·2	19	5·8	94·5	25	6·6	94·2	14	3·9	96·9
	312+	17	5·8	100·0	18	5·5	100·0	22	5·8	100·0	11	3·1	100·0
	Total ..	292	100·0		327	100·0		377	100·0		356	100·0	
Other Women	1–3	4	1·1	1·1	4	1·0	1·0	4	0·9	0·9	5	1·3	1·3
	4–6	18	5·0	6·1	23	5·8	6·8	33	7·4	8·3	31	7·8	9·1
	7–12	76	21·2	27·3	64	16·1	22·9	80	18·1	26·4	88	22·3	31·4
	13–18	56	15·6	42·9	65	16·4	39·3	54	12·2	38·6	60	15·2	46·6
	19–24	37	10·3	53·2	43	10·8	50·1	38	8·6	47·2	48	12·2	58·8
	25–48	59	16·5	69·7	85	21·4	71·5	106	23·9	71·1	97	24·5	83·3
	49–78	45	12·6	82·3	43	10·8	82·3	44	9·9	81·0	24	6·1	89·4
	79–156	27	7·6	89·9	39	9·8	92·1	38	8·6	89·6	19	4·8	94·2
	157–312	7	2·0	91·9	16	4·1	96·2	20	4·5	94·1	10	2·5	96·7
	312+	29	8·1	100·0	15	3·8	100·0	26	5·9	100·0	13	3·3	100·0
	Total ..	358	100·0		397	100·0		443	100·0		395	100·0	

Table IV shows that the number of spells lasting more than one year are centred in the older age groups, and it is of interest to note that (in contrast to the inception rates) these overall long-term spells per 1,000 persons exposed to risk are higher for other women than for men. This is probably due to the large proportion of other women in the younger age groups where the inception rates are low. The overall rate for married women is more than double that for either men or other women. Here the age-specific rates are of much interest.

For the last year under review it was possible to extract the arthritis and rheumatism cases for the Belfast Local Office area of the Ministry of Labour for comparison with the experience in the rest of the Province. Unfortunately an age and sex distribution of the population exposed to risk in the Belfast area was not available—only the totals for men and for women.

The inception rates per 1,000 exposed to risk for spells commencing during the year were as follows:

Area	Sex	
	Men	Women
Belfast	17·4	21·7
Rest of Province	39·0	24·1
Whole of Northern Ireland	28·2	22·8

The number of spells lasting more than one year per 1,000 exposed to risk were as follows:

Area	Sex	
	Men	Women
Belfast	1·0	2·8
Rest of Province	3·8	4·3
Whole of Northern Ireland	2·7	3·5

In considering the reasons for this striking difference for men in the two areas, one has to consider, among other things, the age and sex differential of those exposed to risk in the two areas and the differing occupational backgrounds and social conditions.

While the Tables largely confirm clinical impressions regarding age incidence and chronicity, a striking and unexpected feature is the relatively high incidence of this disease group in married women compared with other women and with men, notably in the age group 20-29 years. This may well reflect only the high incidence of sickness generally amongst married women as a class which was shown by Park and Kidd (1958). It is possible that some of this sickness absence is due to social or domestic causes rather than to clinical disability, and it may be that "rheumatism" in a proportion of cases is a conventional diagnostic label.

TABLE IV

NUMBER OF SPELLS OF ARTHRITIS AND RHEUMATISM LASTING MORE THAN A YEAR, BY AGE GROUP, AND SEX AND RATE PER 1,000 EXPOSED TO RISK (20 PER CENT. SAMPLE)

Sex and Marital Status	Age Group (yrs)	1954/55		1955/56		1956/57		1957/58	
		No.	Rate	No.	Rate	No.	Rate	No.	Rate
Men	20–29	3	—	—	—	4	—	2	—
	30–39	8	0·5	11	0·9	6	0·4	4	0·3
	40–49	21	1·4	32	2·2	25	1·7	19	1·3
	50–59	90	7·2	92	7·4	92	7·4	88	6·9
	60–64	62	13·4	76	16·7	73	15·2	69	14·1
	Total	184	2·7	211	3·1	200	2·9	182	2·7
Married Women	20–29	5	2·8	3	1·2	1	0·4	—	—
	30–39	4	2·1	4	2·1	4	2·4	3	1·7
	40–49	22	11·0	95	7·5	14	7·4	17	8·9
	50–59	35	25·6	40	28·6	28	20·0	28	18·7
	60–64								
	Total	66	8·2	62	7·8	47	5·9	48	5·9
Other Women	20–29	3	0·4	3	0·4	3	0·4	2	0·3
	30–39	9	3·0	8	2·7	5	1·7	5	1·7
	40–49	19	7·3	22	7·9	14	5·4	11	4·6
	50–59	53	18·9	48	17·1	46	16·4	47	16·2
	60–64								
	Total	84	3·6	81	3·5	68	2·9	65	2·9

Climatic conditions in Northern Ireland with its high rainfall may be considered by some to have an influence on the incidence of arthritis and rheumatism, but this is a factor difficult to measure. Occupation as an influence is also highly relevant and it is hoped that a general survey of morbidity by occupation will be possible using data from the 1961 population census of Northern Ireland as the basis of the population exposed to risk.

Comment

This study gives a broad indication of the size of this disease group in the insured working population of Northern Ireland.

From a purely economic point of view the chronic rheumatic diseases are one of the major causes of absenteeism in industry. In Great Britain it is said that almost 28 million days are lost annually through these diseases at a cost to industry of £80 million. These figures, produced by the Empire Rheumatism Council, are significant only in indicating the economic size of the problem. In Northern Ireland it is felt that the situation is proportionately as great as in Great Britain. In the year ending May 31, 1958, it is estimated that chronic rheumatism accounted for 1,030,000 working days lost to industry. This is a heavy and significant burden on the economy of a small community such as Northern Ireland.

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Arthrite et rhumatisme parmi la population de l'Irlande du Nord

RÉSUMÉ

Cette étude offre une indication générale de l'importance de ce groupe de maladies parmi la population ouvrière assurée de l'Irlande du Nord. La fréquence élevée de ces maladies chez des hommes de la région de Belfast, où réside à peu près la moitié de la population de l'Irlande du Nord, par rapport à celle chez des hommes du reste du pays, est significative. Tandis que les tables de morbidité, durée et incapacité prolongée confirment en général les impressions médicales concernant l'âge, la fréquence et la chronicité, on est frappé par le nombre relativement élevé des ouvrières mariées, surtout de celles âgées de 20 à 29 ans, parmi les malades. Cela pourrait bien réfléchir seulement la fréquence élevée de la maladie en général parmi des femmes mariées, fait mentionné dans un article antérieur. Certaines de ces absences du travail pourraient bien être dues à des raisons sociales et de famille plutôt qu'à l'incapacité d'ordre pathologique.

Artritis y reumatismo entre la población asegurada de Irlanda del Norte

SUMARIO

Este artículo presenta una indicación general de la frecuencia de este grupo de enfermedades entre la población obrera asegurada de Irlanda del Norte. La elevada incidencia de estas enfermedades entre adultos varones en el area de Belfast, donde reside alrededor de la mitad de la población asegurada de Irlanda del Norte, en comparación con la encontrada entre los varones del resto del pais es significativa. Mientras que los valores en cuanto a comienzo, duración e incapacidad temporal confirman las impresiones clínicas respecto a edad, incidencia y cronicidad, es de lo más llamativo la relativamente alta frecuencia de presentación de este grupo de enfermedades entre las trabajadoras casadas, especialmente entre aquellas con una edad comprendida entre 20 y 29 años. Esto podía muy bien ser un reflejo solamente de la alta incidencia de enfermedades entre las mujeres casadas, lo que fué señalado en una publicación anterior. Algunas de estas ausencias del trabajo podian obedecer más a causas sociales y domésticas que a incapacidad patológica.

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ON THE NATURE OF THE RHEUMATOID FACTOR*

BY

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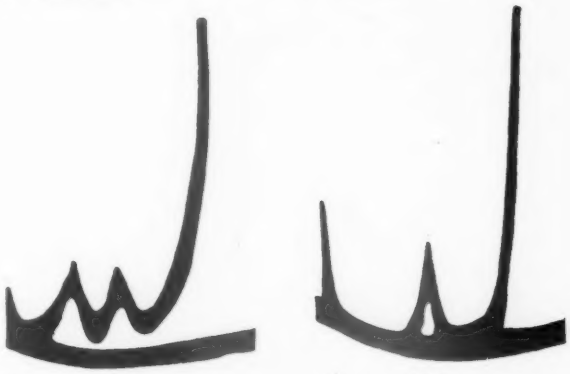
The researches initiated by Cecil, Nichols, and Stainsby (1931), Waaler (1940), and Rose, Ragan, Pearce, and Lipman (1949) on the agglutinating activity of serum from patients with rheumatoid arthritis led to the discovery of a serum factor, now regarded as characteristic of rheumatoid arthritis, and therefore designated "rheumatoid factor" (Pike, Sulkin, and Coggeshall, 1949; Svartz, 1956, 1959). This factor is important not only in differential diagnosis but also because it may take part in the pathogenesis of rheumatoid arthritis.

The rheumatoid factor has been located in the globulin fraction (Waaler, 1940), in Cohn's "Fraction III" (Heller, Kolodny, Lepow, Jacobson, Rivera, and Marks, 1955) and in the euglobulin fraction (Lamont-Havers, 1955; Svartz, Carlson, Schlossmann, and Ehrenberg, 1958; Svartz and Schlossmann, 1955); electrophoretically, it migrates with the gamma-globulin.

With the ultracentrifuge, the gamma-globulin fractions of normal serum can be shown to consist of two components, one having a sedimentation constant of 19 Svedberg units (19 S gamma-globulin) and a molecular weight of about 900,000, the other having a sedimentation constant of 7 Svedberg units (7 S gamma-globulin) and a molecular weight of about 156,000 (Cohn, 1947; Müller-Eberhard, Kunkel, and Franklin, 1956; Müller-Eberhard, Franklin, and Kunkel, 1957; Pedersen, 1945; Wallenius, Trautman, Kunkel, and Franklin, 1957). The 19 S fraction amounts to only 5 per cent. of the total gamma-globulin. Müller-Eberhard (1959) and Schultze (1957) have demonstrated that the carbohydrate content of the 19 S component is four times higher than that of the 7 S component.

In the sera from rheumatoid patients, a component having a sedimentation constant of 22 Svedberg units has been detected (Fig. 1) (Franklin, Holman, Müller-Eberhard, and Kunkel, 1957; Franklin, Kunkel, Müller-Eberhard, and Holman, 1957; Franklin and Kunkel, 1957; Müller-Eberhard and others, 1956). Franklin and Müller-Eberhard and their co-workers have shown that this component is responsible for the positive agglutination reaction. They also demonstrated that the 22 S component represents a complex of 19 S and 7 S gamma-globulin in the ratio of 43 : 57 per cent.; and they conclude that there is one heavy for every six light molecules of gamma-globulin. Serological activity thus appears to be characteristic of the 19 S fraction.



(*a*) (*b*)

Fig. 1.—Comparison of ultracentrifugal patterns in normal and rheumatoid serum:
(*a*) Serum from a patient with rheumatoid arthritis, showing two components which sediment quickly, the physiological 19-S fraction and the pathological 22-S;
(*b*) Normal serum under same conditions (according to Müller-Eberhard, Kunkel, and Franklin, 1957).

Studies utilizing zone electrophoresis, chromatography in cellulose columns and ultracentrifugation confirm that the rheumatoid factor is a macromolecular gamma-globulin of the 19 S type with

* Report to the IV European Congress of Rheumatology in Istanbul, September, 1959.

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a molecular weight of 900,000 (Franklin and others, 1957; Müller-Eberhard and others, 1956, 1957; Svartz, 1956, 1959; Svartz and others, 1955, 1958). According to Svartz (1959), it contains approximately 9 per cent. carbohydrate.

Apart from its serological reactivity the rheumatoid 19 S gamma-globulin reacts physically and chemically in the same way as normal 19 S gamma-globulin (Müller-Eberhard, 1959; Müller-Eberhard and others, 1957). Müller-Eberhard (1959) believes however, that a difference in molecular structure may account for the serologic reactivity.

It was therefore considered worth while to carry out a detailed chemical analysis of the rheumatoid factor.

Method

Pure rheumatoid factor was obtained by precipitation with gamma-globulin in the following way:

Serum from rheumatoid patients having high titres in erythrocyte and latex-fixation tests was mixed in 50 ml. aliquots with the same volume of a solution of gamma-globulin* and the mixture was added to borate buffer (pH 8·0) to give a concentration of 0·5 per cent. After 2 hours at room temperature and a further 46 hours at 4° C., the resultant precipitate was separated by centrifugation at 17,000 r.p.m. for 20 min. The precipitate was washed three times with distilled water and dried to a constant weight over concentrated sulphuric acid. To obtain a sufficient amount of precipitate, serum samples from five different patients were pooled.

The experiments of Müller-Eberhard have shown that the 7 S and 19 S fractions (Fig. 2) are in a ratio of 1 : 1 in a solution of the precipitate in the ultracentrifuge; aggregates with 35 S and 150 S were also observed which derived from the 7 S gamma-globulin added for the precipitation. According to a personal communication from Müller-Eberhard, the gamma-globulin aggregates were found to amount to 50-70 per cent. of the total precipitate if the gamma-globulin was first heated. In the present experiments the gamma-globulin has not been heated. A solution of the precipitate in 5-M urea was repeatedly centrifuged at 20,000 r.p.m. for periods of up to 3 hours and the above mentioned aggregates were found to comprise 40 per cent. of the total precipitate. In repeated tests this component showed no serological activity. It was concluded that 70 per cent. of the precipitate consists of 7 S gamma-globulin, the remainder being 19 S gamma-globulin and corresponding to the rheumatoid factor. This ratio permits the two components to be estimated separately.

Fig. 2.—Analytical ultracentrifugal diagram of a precipitate solved in 5-M urea, which was gained by charging the serum of a rheumatoid patient with gamma globulin heated for a short period. The sedimentation coefficient of the quick component amounts to 19 S and that of the slow one to 7 S.

* Behringwerke, Marburg.

Colorimetric analyses of the carbohydrate were carried out. Hexoses were determined by the methods of Holzman, MacAllister, and Niemann (1947) and Winzler (1955); fucose by the method of Jacubeit, Brünger, and Knedel (1959); hexosamine by that of Dische and Borenfreund (1950); neuramine (sialic acid)† by that of Schultze, Schmidtberger, and Haupt (1958); the polysaccharide was estimated by the tryptophane reaction (Shetlar, Foster, and Everett, 1948) and the total nitrogen by the method of Kjeldahl (Hallmann, 1950). The amino acids were determined by the method of Moore and Stein (1948) after protein hydrolysis (Zahn, 1954), and elution from a two-way paper chromatogram (Levy and Chung, 1953).

Results

Table I (opposite) shows the carbohydrate content of the rheumatoid factor, and normal 7 S and 19 S gamma-globulin.

The polysaccharide content of 7 S found by Müller-Eberhard and his co-workers (1956, 1957, 1959) is relatively low; the hexoses seem to be highest followed by hexosamine, fucose, and neuramine in that order. By comparison with 7 S, the normal 19 S fraction presents a threefold increase in the polysaccharide content, a fourfold increase in hexoses, a twofold increase in fucose, and a sevenfold increase in neuramine.

The total carbohydrate content of the rheumatoid factor (10·78 per cent.) found by us is higher than the 9 per cent. reported by Svartz (1959). Our results for the carbohydrate components of the rheumatoid factor seem to correspond closely with those obtained by Müller-Eberhard for normal 19 S gamma-globulin.

Corresponding with the increased carbohydrate content, the total nitrogen content of the rheumatoid

† We are obliged to Dr. Brossmer of the Max Planck Institution for Medical Research, Sect.: Chemistry (Director: Dr. R. Kuhn, Heidelberg) for letting us have sialic acid with which to make calibration curves.

TABLE I

CARBOHYDRATE CONTENT OF RHEUMATOID FACTOR (FRACTION $S_{20} = 19$ S) COMPARED WITH NORMAL GAMMA GLOBULIN (FRACTIONS $S_{20} = 7$ S AND $S_{20} = 19$ S)

Fraction		Normal Gamma Globulin				Rheumatoid Factor
		$S_{20} = 7$ S		$S_{20} = 19$ S		$S_{20} = 19$ S
Authors and Dates		(Müller-Eberhard, 1959)	(Wöhler and others, 1960)	(Müller-Eberhard, 1959)	(Schultze)	(Wöhler and others, 1960)
Carbohydrate Content (per cent.)	Hexose	1·22	1·23	5·2	4·16	5·13
	Fucose	0·29	0·3	0·62	0·46	0·85
	Hexosamine	1·14	1·2	2·9	2·4	2·9
	Neuramine Acid	0·22	0·25	1·7	1·81	1·84
	Polysaccharide	2·58	2·7	9·8	8·83	10·78

factor is smaller than the 7 S gamma-globulin, 14·7 g. per cent. as against 16·03 g. per cent. (Table II, overleaf).

When the two-way paper chromatography was applied after hydrolysis of protein, a large series of amino acids could be proved (Fig. 3).

The quantitative values of the amino acids in the rheumatoid factor and in 7 S gamma-globulin are shown in Table II. We used the amino acid composition of 7 S gamma-globulin (Brand, 1946; Brand, Kassell, and Saidel, 1944) for comparison because, according to Franklin and others (1957), Heimer (1959), and Heimer and Federico (1958), decomposition of the intermolecular S-S links of the rheumatoid factor is accompanied by a depolymerization into units of 7 S gamma-globulin; repolymerization may be prevented by adding monoiodine acetate (Isliker, 1958; Heimer, 1959; Heimer and Federico, 1958).

Glutamic acid comes first with about 13 per cent., followed by aspartic acid, valine, threonine, lysine, proline, leucine, serine, tyrosine, and so on. While in general the values seem to be somewhat lower in the rheumatoid factor, the values in the rheumatoid factor for cysteine and cystine are higher than in the 7 S gamma-globulin. The higher cystine value may be an expression of the increased S-S links which might be expected from the findings of Franklin and

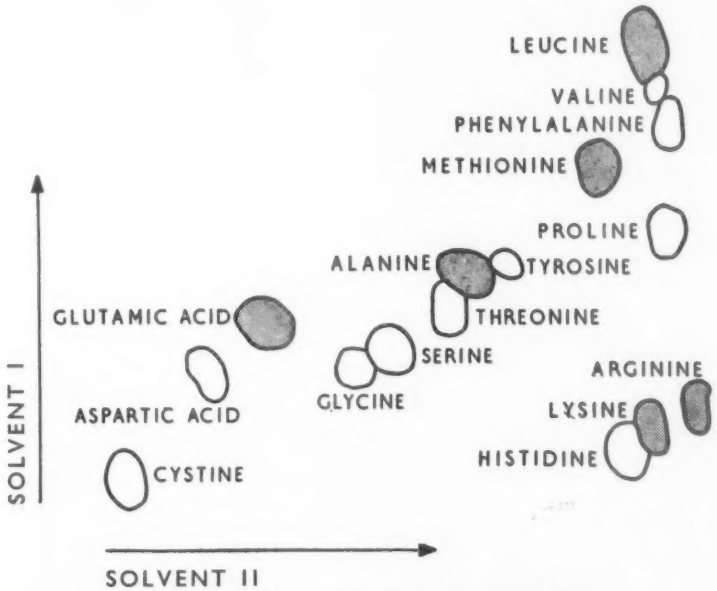

Fig. 3.—Two-way chromatogram of the rheumatoid factor.
Presentation of the amino acids with ninhydrine:
Solvent I: Isopropanolformic acid-glacial acetic acid-water, 500 : 105 : 105 : 105;
Solvent II: Phenol-water mixture, 5 : 1.

TABLE II

COMPOSITION OF AMINO ACIDS, AMOUNT OF NITROGEN, AND MOLECULAR WEIGHT OF RHEUMATOID FACTOR (S 19 FRACTION) COMPARED WITH NORMAL GAMMA GLOBULIN (S-7 FRACTION)

Globulin Fraction		Normal Gamma Globulin (S_{20} = 7 S)	Rheumatoid Factor (S_{20} = 19 S)
Molecular Weight		(Cohn, 1957) 156,000	(Müller-Eberhard, 1959) 900,000
Total Nitrogen (per cent.)		(Brand, 1946) 16·03	(Wöhler and others, 1960) 14·7
Amino Acids (per cent.)	Glycine	(Brand, 1946) 4·2	(Wöhler and others, 1960) 3·6
	Alanine	2·2	2·0
	Valine	9·7	8·2
	Leucine	9·3	7·3
	Isoleucine	2·7	2·3
	Proline	8·1	7·6
	Phenylalanine	4·6	4·5
	Cysteine	0·7	0·99
	Cystine	2·37	3·4
	Methionine	1·06	1·1
	Tryptophan	2·86	2·7
	Arginine	4·8	4·2
	Histidine	2·5	3·0
	Lysine	8·1	7·7
	Aspartic acid	8·8	9·6
	Glutamic acid	11·8	13·1
	Serine	11·4	7·3
	Threonine	8·4	8·2
	Tyrosine	6·75	7·0

others (1957) regarding depolymerization of the rheumatoid factor. Although the amino acid percentage composition of the rheumatoid factor and normal 7 S gamma-globulin appear to be similar, one cannot be certain that the quantitative values are identical.

The present results have enabled the carbohydrate content and the amino acid composition of the rheumatoid factor to be established. Since its carbohydrate content resembles that of the normal 19 S gamma-globulin fraction and its amino acids correspond with 7 S gamma-globulin, this protein and 19 S may be closely related. Which physicochemical correlate the serological activity is based on cannot be decided. Examination of the active end-groups might help to elucidate this problem.

Summary

Chemical analyses have been made on the rheumatoid factor isolated by precipitation with gamma-globulin. The carbohydrate content of the rheumatoid factor is similar to that of normal 19 S gamma-globulin: hexose 5·13 per cent., fucose 0·85 per cent., hexosamine 2·9 per cent., and neuramine 1·84 per cent. The percentage amino acid composition of the rheumatoid factor was similar to that of normal 7 S gamma globulin.

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Sur la nature du facteur rhumatismal

RÉSUMÉ

Le facteur rhumatismal, isolé par précipitation avec la globuline gamma, fut soumis à l'analyse chimique. Le contenu en hydrates de carbone du facteur rhumatismal est similaire à celui de la globuline gamma 19 S normale: hexose 5,13%, fucose 0,85%, hexosamine 2,9% et neuramine 1,84%. Le pourcentage des amino-acides dans le facteur rhumatismal fut similaire à celui de la globuline gamma 7 S normale.

Sobre la naturaleza del factor reumatoide

SUMARIO

El factor reumatoide, aislado por precipitación con la globulina gama, fué sometido al análisis químico. El contenido en hidratos de carbono del factor reumatoide es similar al de la globulina gama 19 S normal: hexosa 5,13%, fucosa 0,85%, hexosamina 2,9% y neuramina 1,84%. La proporción de los amino-ácidos en el factor reumatoide fué similar a la en la globulina gama 7 S normal.

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NAIL STUDIES IN RHEUMATOID ARTHRITIS*

BY

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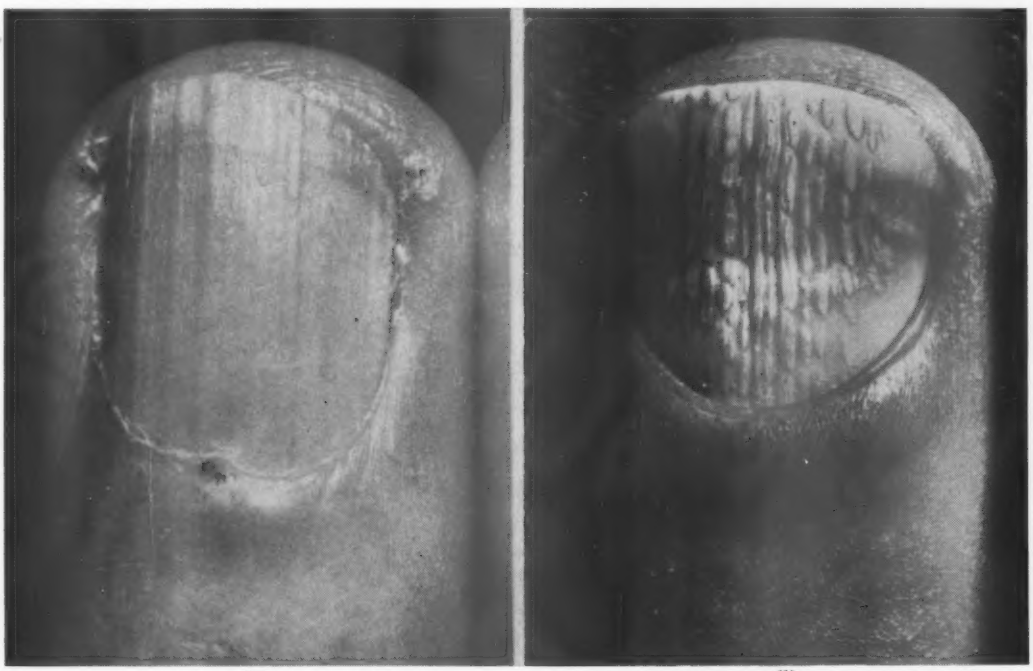
Nail changes have been recognized for many years in patients suffering from rheumatoid arthritis (Garrod, 1890; Bannatyne, 1898), but there have been few attempts to estimate their frequency (Short, Bauer, and Reynolds, 1957). Pronounced longitudinal ridges, which often have a beaded appearance, were observed to be a common though non-specific phenomenon in these patients, and the impression had been formed that they occurred at an earlier age than in the general population. Such changes have been described as nail atrophy, but dystrophy is perhaps a better description.

* Paper read at a meeting of the Heberden Society on December 4, 1959.

Incidence and Type of Nail Changes

In order to collect further information, a survey has been made of the nail appearances in 186 consecutive patients with rheumatoid arthritis seen during a one-year period. All had a chronic polyarthritis with a positive Rose-Waaler test, and they were of both sexes in the proportion of one male to four females. The findings in this group were compared with those in 186 hospital in-patients of roughly similar age and sex distribution.

Personal observation was made of all the finger nails of both hands, and longitudinal ridging if present was graded as slight or severe (Fig. 1).



(*a*)

Fig. 1*a*.—Slight nail ridging in rheumatoid arthritis; note presence of nail-fold vascular lesion.

(*b*)

Fig. 1*b*.—Severe nail ridging in rheumatoid arthritis.

A record was made of any nails that had been subjected to trauma, and the findings in these nails were not included in the final analysis.

Results.—The incidence of severe ridging and beading, as judged in two or more nails, was higher in the patients with rheumatoid arthritis, in all age groups, than in the controls, but in both the rheumatoid and the control groups, it increased with age (Table I).

TABLE I

INCIDENCE OF TROPHIC NAIL CHANGES WITH AGE

Age Group (yrs)	Rheumatoid Arthritis		Controls	
	No. of Cases	Percentage Beading + Severe Ridging	No. of Cases	Percentage Beading + Severe Ridging
20–29	13	0	20	0
30–39	25	4	19	0
40–49	36	11	34	3
50–59	51	26	34	18
60–69	47	53	40	27
Over 70	14	57	39	33

It has been suggested that nail changes are related to duration of disease activity (Short, Bauer, and Reynolds, 1957), but in this study the relationship is less clear-cut than that with age (Table II).

TABLE II

INCIDENCE OF TROPHIC NAIL CHANGES WITH DURATION OF RHEUMATOID ARTHRITIS

Duration (yrs)	No. of Cases	Percentage Beading + Severe Ridging
0–5	74	24
6–10	50	24
11–15	30	37
Over 15	28	32

Other abnormalities noted during the course of the survey are shown in Table III. There was a definite increase in the incidence of palmar flushing, such as is frequently seen in liver disease and in pregnancy, and in four patients it was associated with marked redness of the finger tips. Nail-edge or nail-fold vascular lesions similar to those previously described by Bywaters (1949, 1957) were seen in ten cases, and in seven they were associated with severe ridging and beading. Transverse ridging, which was usually confined to a single nail, and leuconychia were not more common in the rheumatoid group. Thickening and discolouration of the nails and atrophy of the skin of the fingers were common but difficult to assess.

TABLE III

PERCENTAGE INCIDENCE OF ABNORMALITIES OTHER THAN RIDGING AND BEADING

Abnormality	Rheumatoid Arthritis	Controls
Palmar Flush	8	0·5
Vascular Lesions	5·5	0·5
Transverse Ridging	4	5
Leuconychia	4	3
Varicosities on Fingers	2	0
Unexplained Clubbing	1	0
Pitting of Nails	0·5	0

One case merits a more detailed description.

A woman aged 65 had suffered from severe rheumatoid arthritis for 30 years, and her nails consisted of yellow, heaped-up, crusted material, which was shed at intervals (Fig. 2, opposite). *Post mortem* section revealed extreme keratin formation with abscesses underlying the nail plate and marked endarteritis of the nail-bed vessels (Fig. 3, opposite). The possibility that this was a case of pustular psoriasis in association with rheumatoid arthritis was considered, but the patient had a positive Rose-Waaler test, and there was no psoriasis of the skin, and none of the features of psoriatic arthropathy (Wright, 1959). The macroscopic appearances were similar to those described in some cases of Reiter's syndrome by Montgomery, Poske, Barton, Foxworthy, and Baker (1959) and in four cases of keratoconjunctivitis sicca by Thompson and Eadie (1956).

The cause of the longitudinal nail ridges and their frequent beaded appearance is unknown. It has been observed that following removal of a nail, when growth is resumed, the ridges reappear in the same position as before. Lewis (1954) and Lewis and Montgomery (1955) cited evidence that the dorsal surface of the nail may be formed from the roof of the nail-fold, and described in the senile nail-fold keratinizing whorls of generative cells which they thought to be responsible for the ridging. Samman (1959), by a dye injection technique, has demonstrated the presence of capillary loops in the roof of the nail-fold. It is possible that changes in these vessels may be responsible for the nail dystrophy in rheumatoid arthritis, and it is interesting that there was a high incidence of such changes in those patients who showed nail-edge or nail-fold vascular lesions. Lewis, in his studies on the senile nail, found thickening of the vessel walls in the nail generative areas, and Sunderland and Ray (1952) have shown reduced nail growth following arterial ligation.

Another possibility is that the changes might be present more frequently in proximity to involved

Fig. 2.—Unusual nail dystrophy in a case of rheumatoid arthritis of 30 years' duration.

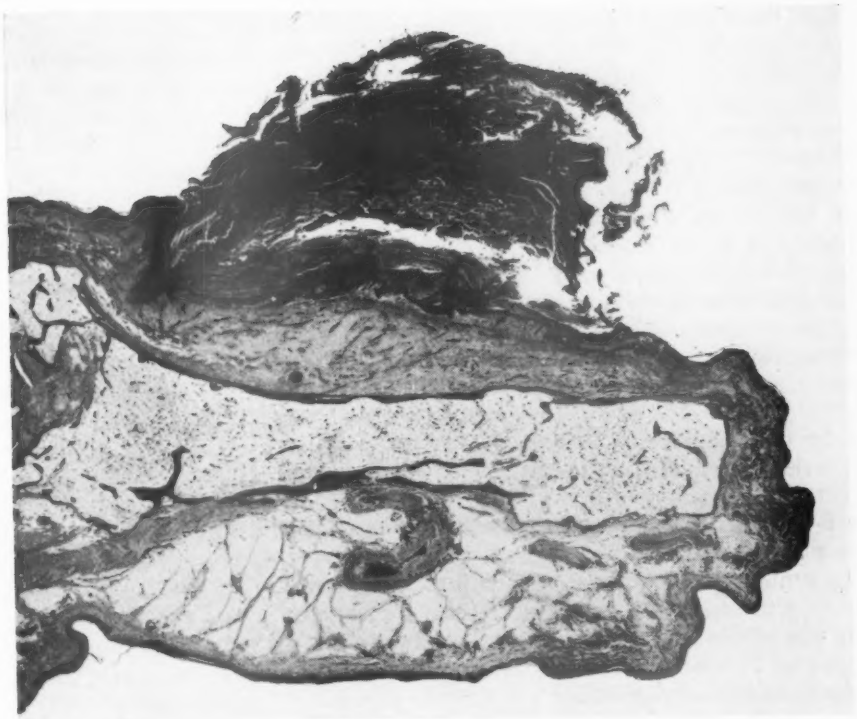


Fig. 3.—Section of nail-bed of case shown in Fig. 2.

joints, as is the case of the nail lesions in psoriatic arthropathy (Wright, 1959). This was not borne out by the survey, as no terminal interphalangeal joints were involved, and when present the changes usually occurred in all the finger nails.

Disuse is a further factor to be considered and one patient with a long-standing hemiplegia included in the control group showed nail changes on the affected hand only. Mitchell (1871) and Head and Sherren (1905) found retarded nail growth on the fingers of a paralysed hand, and similar retardation occurred when a splint or cast was worn.

Nail Growth

Now that more accurate methods of measurement have been developed it was felt that observations on nail growth might throw light on the problem, and these have been made in both children and adults using a modification of the photographic technique of Babcock (1955).

The cases studied consisted of eight girls with Still's disease under the age of 11 and fifteen adult females with rheumatoid arthritis, all of whom were undergoing in-patient treatment. The activity of their disease varied in severity and five in each group were on systemic steroids. The nail growth rates were compared with those of thirteen children convalescing from rheumatic fever, who had normal sedimentation rates, and twenty adult female members of the hospital staff, who showed a similar age distribution to the patients with rheumatoid arthritis.

A mark was made on the lunula of both thumbs with a sharp scalpel and this was then rubbed over with black paint. Further marks were made at weekly or fortnightly intervals for at least 6 weeks. A 35-mm. miniature camera with a fixed close-up extension was used to give a magnified image for recording on film. Fixed to the end of the camera extension was a bracket to enable the finger nail to be correctly positioned against a glass frame, and it was recorded by flashlight. This record was measured in an Ediswan micro-reader which enlarged it thirty times.

In order to ascertain a possible source of error the apparatus was dismantled and reassembled seven times between exposures on the same nail. These negatives were enlarged and superimposed and no error could be detected. Observer error was 2 per cent., and the average error in adding together a series of readings on the same nail at weekly or fortnightly intervals was less than 1·5 per cent. over a 6-week period. The greatest source of error was in making the horizontal scratch mark exactly on the lunula. This error would be reduced by only having to make a mark on the lunula at the start of our observations, but we were unable to show up the lunula on our negatives with sufficient clarity to make this possible.

Results.—The mean daily nail growth rate, measured over a 6-week period in healthy female adults was 0·09 mm. per day, in adult females with rheumatoid arthritis 0·085 mm. per day, in convalescent cases of rheumatic fever under the age of eleven 0·117 mm. per day, and in Still's disease 0·115 mm. per day (Table IV).

There were wide variations in growth rate between individuals, but for any one individual the rate remained relatively constant over the 6-week period. The rate of growth in the cases with Still's disease and rheumatoid arthritis, when the groups were taken as a whole, fell within the normal range of the comparable controls, but in children convalescing from rheumatic fever and in children with Still's disease it was significantly faster than in the adults (Fig. 4, opposite).

TABLE IV

DAILY NAIL GROWTH (mm./day)

Subjects	Adult Females		Children aged 11 yrs or Less	
	Healthy	Rheumatoid Arthritis	Still's Disease	Convalescing after Rheumatic Fever
Daily Growth (mm.)	·108 ·105 ·101 ·100 ·098 ·096 ·096 ·095 ·094 ·094 ·09 ·088 ·088 ·087 ·086 ·085 ·084 ·076 ·07 ·064	·106 ·100 ·092 ·090 ·090 ·089 ·087 ·082 ·082 ·082 ·080 ·074 ·072 ·069 ·066	·158 ·124 ·118 ·109 ·108 ·105 ·099 ·098	·158 ·147 ·126 ·123 ·122 ·117 ·115 ·109 ·105 ·104 ·104 ·103 ·086
Average ..	·090	·084	·115	·117

No correlation was found between trophic nail changes and nail growth rate, but the latter was retarded in three cases who had very severe generalized disease activity. This is well seen in one case (Fig. 5, opposite) in which the depression in growth rate preceded the increase in prednisone dosage and returned to normal when the disease activity was brought under control.

In two cases with local disease activity, the rate was not affected by the proximity of the involved joints. One was a girl aged 13 with psoriatic arthritis, three of whose terminal interphalangeal joints were involved, and the other a patient with rheumatoid arthritis who had unilateral wrist-joint involvement.

Discussion

The development of a photographic technique by Babcock (1955) has allowed nail measurements to be made with greater accuracy and at shorter time-intervals than with previous methods. Satisfactory results using this method have recently been reported by Sibinga (1959). The results reported here are at variance with those of Sibinga

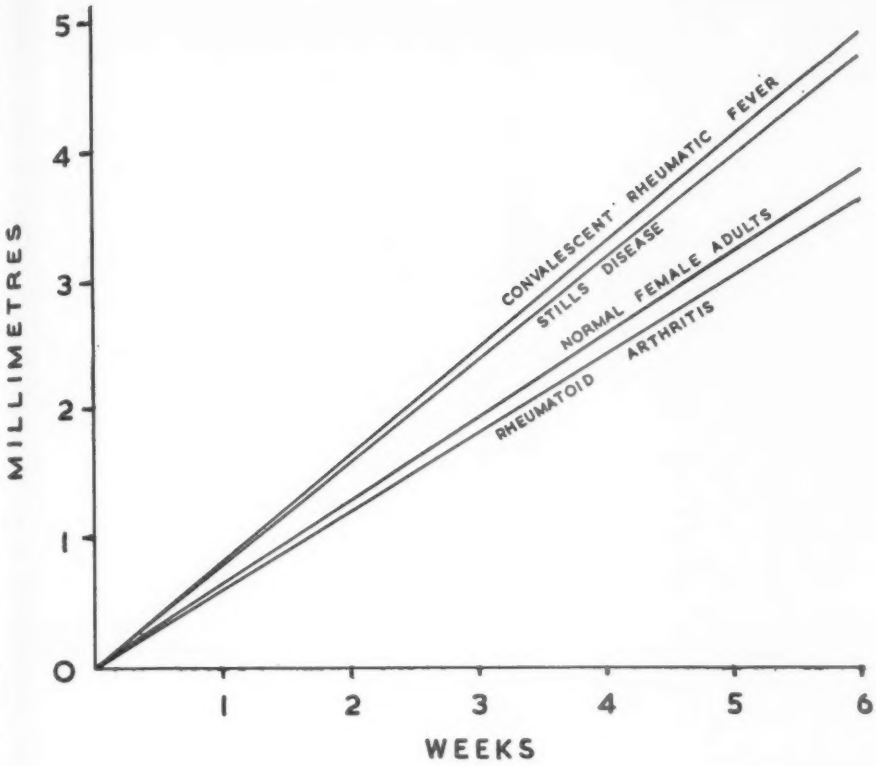


Fig. 4.—Average nail growth rates in Still's disease, rheumatoid arthritis, convalescent rheumatic fever, and normal female adults.

in that there was a significant decrease in nail growth rate with age, when the rates in children were compared with those in adults ($P<0{\cdot}001$), but they confirm that there is a wide range of normal nail growth between different individuals of the same age.

Clark and Buxton (1938) showed a pronounced seasonal variation in nail growth rate, and Geoghegan, Roberts, and Sampford (1958) have reported retarded nail growth in men working in the Arctic. Most of the present observations were made in the spring and early summer, but in two children with Still's disease no difference could be found between their winter and summer rates. This is perhaps hardly surprising as the ward was centrally heated during the colder weather.

Two of the three cases with severe disease activity in whom nail growth rate was retarded were on systemic corticosteroid therapy, and this remains a possible contributory factor, but one which it is difficult to assess. Ansell and Bywaters (1956) have shown that both disease activity and corticosteroid therapy affect growth in height in Still's disease, and Godwin (1959) found that 5 mg. cortisone retarded nail growth in rats. In the case illustrated in Fig. 5 (overleaf), nail growth slowed before the dose of prednisone was increased and returned to normal despite the higher dose, once the disease activity came under control. This retardation could be related to the body temperature, and Sibinga (1959) found nail growth arrest in 23 patients with measles in whom the body temperature exceeded 103° F.

Summary

(1) Nail changes in 186 patients with rheumatoid arthritis have been compared with those in a hospital population. The incidence of severe longitudinal ridging is increased in each age group, and would appear to be related to the age of the patient rather than to the duration of disease activity.

(2) Nail growth measurements have been made over a 6-week period in patients with Still's disease and rheumatoid arthritis, and these have been compared with those in children convalescing from rheumatic fever and in normal adult females. Growth was significantly faster in children than in adults, but taken as a whole the rates in the two groups of patients fell within the normal range. In three patients with very severe generalized disease activity, nail growth rate was retarded, but in two

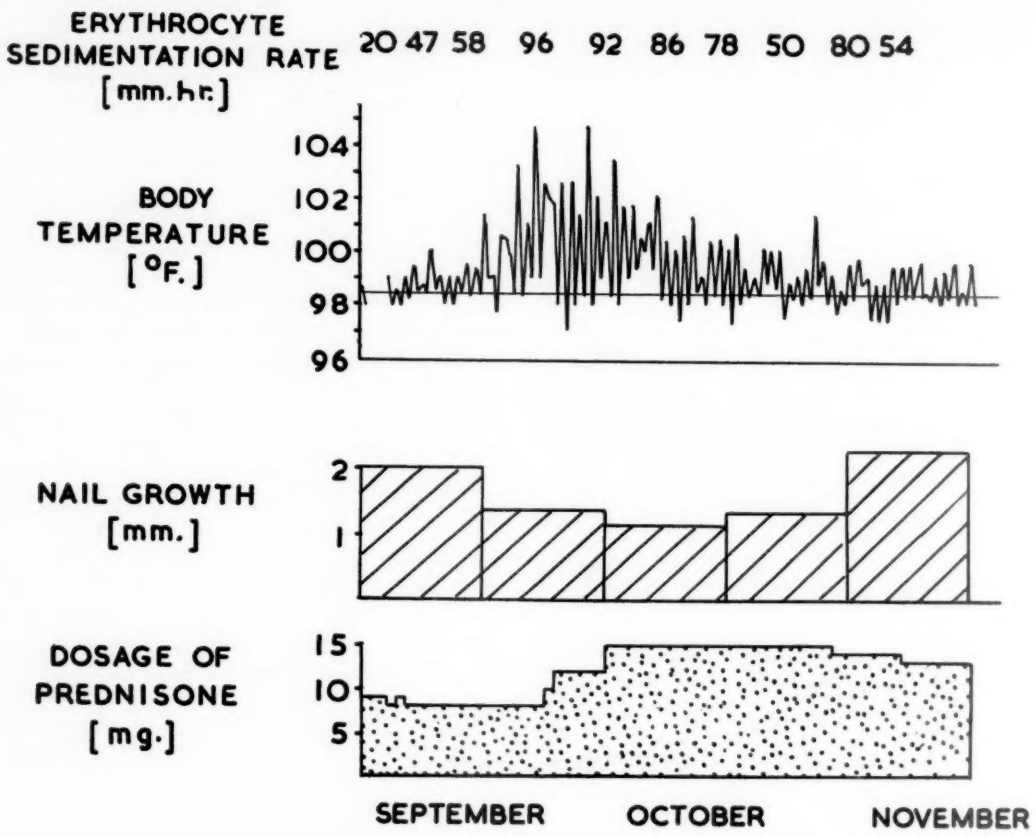


Fig. 5.—Depression of nail growth in active Still's disease in a child aged 7 years.

patients studied it was not affected by the presence of local joint disease.

I should like to thank Prof. E. G. L. Bywaters for permission to study patients under his care and for his friendly advice and criticism, and Mr. Peter Fiske, the Chief Photographer at Taplow, without whose expert assistance this work would not have been possible.

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Discussion

DR. O. SAVAGE (*London*) asked whether there was any association between growth in children and the growth of nails. Dr. B. Ansell has shown patients with Still's disease on steroids in whom growth in height stopped.

DR. HAMILTON said that they had not seen many cases over a long period (only two cases for more than 8 weeks), so that it was impossible to correlate any change in height with changes in nail growth. It was quite possible that increase in steroid dosage did influence nail growth.

PROF. E. G. L. BYWATERS (*London*) said that he thought that nail growth was similar to hair growth, and this was known to be quicker in hot weather. Dr. Hamilton had tested this by wearing a glove on one hand and then making measurements.

DR. HAMILTON said that the testing had shown no difference.

DR. B. ANSELL (*Taplow*) said that in Still's disease the disease activity slowed growth, but prednisolone in moderate dosage slowed it more. One patient, growing

slowly before prednisolone, stopped growing completely when given steroids. Her nail growth, however, had continued at a fairly constant rate.

DR. W. S. C. COPEMAN (*London*) asked whether there had been any qualitative observations as well as quantitative?

DR. HAMILTON said that patients with beading and ridging did not show a slower rate of nail growth than those without such changes, but no specific qualitative observations had been made.

Etude des ongles dans l'arthrite rhumatismale

RÉSUMÉ

(1) Les altérations dans les ongles de 186 malades atteints d'arthrite rhumatismale furent comparées à celles chez d'autres malades hospitalisés. La fréquence des stries longitudinales prononcées des ongles augmente avec l'âge dans chaque groupe et semble être associée plus à l'âge qu'à la durée de l'activité morbide.

(2) On a mesuré pendant plus de six semaines la croissance des ongles chez des patients atteints de maladie de Still et d'arthrite rhumatismale, et on a comparé les résultats aux chiffres obtenus chez des enfants convalescents de rhumatisme articulaire aigu et chez des femmes normales. La croissance était appréciablement plus rapide chez des enfants que chez des adultes, mais dans l'ensemble elle était similaire et bien normale dans les deux groupes. Chez trois malades avec une activité morbide sévère et généralisée, la croissance était retardée, mais chez deux malades étudiés elle n'était pas affectée par la présence d'une maladie articulaire locale.

Estudio de las uñas en la artritis reumatoide

SUMARIO

(1) Se estudiaron las alteraciones en las uñas de 186 enfermos con artritis reumatoide en relación con las del resto de la población hospitalaria. La incidencia de acusadas strías longitudinales de las uñas aumenta en proporción directa con la edad en cada grupo y parece estar más en relación con la edad del paciente que con la duración de la enfermedad.

(2) Se midió el crecimiento de las uñas durante un período de más de 6 semanas en pacientes con enfermedad de Still y con artritis reumatoide y se compararon los resultados con cifras obtenidas en niños convalecientes de reumatismo poliarticular agudo y en adultos normales del sexo feminino. Dicho crecimiento fué significativamente más rápido en los niños que en los adultos, pero considerando los resultados en conjunto, la proporción de crecimiento en ambos grupos de enfermos está dentro de los límites normales. En tres casos de evolución mórbida grave y generalizada, el crecimiento de las uñas estaba retardado, pero en dos enfermos dicho crecimiento no fué afectado por la presencia de una enfermedad articular localizada.

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ARTICULAR MANIFESTATIONS OF ERYTHEMA NODOSUM*

BY

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Erythema nodosum was first distinguished from other forms of erythema by Willan (1808), and Hebra (1860) amplified Willan's account of the condition as follows:

" . . . tumours of a pale red colour, raised above the level of the skin, and either semi-globular or oval in form. These swellings are tender on pressure, and are observed chiefly on the lower limbs. In some cases, the outbreak of this form of erythema is preceded by slight febrile disturbance, and even by shivering. . . . They have at first a pale rose red colour, with a slight tinge of yellow. Afterwards they become dark red, then livid; and when the red colour has faded, a yellowish coloration remains for a considerable time."

Neither author mentioned arthritic manifestations, but Mackenzie (1886) reported a study of 108 cases of erythema nodosum in 34 of whom there were symptoms of joint involvement. Various authors have subsequently confirmed the association. Löfgren (1946) reviewed 178 cases of erythema nodosum; 57 per cent. of his patients complained of painful joints at the outset, and 27 per cent. had actual joint swelling. In this series Löfgren classified the aetiology as tuberculous in 104 patients and as streptococcal in thirty. In a subsequent investigation (Löfgren, 1953a), he studied 212 patients with bilateral hilar gland enlargement associated with a negative or weakly positive reaction to tuberculin; 113 of them had erythema nodosum as a presenting symptom, 101 with arthralgia and 78 with actual joint swelling. James (1959) analysed 200 patients with histological evidence of sarcoidosis in the form of non-caseating giant-cell systems; 62 of them (31 per cent.) had erythema nodosum and of these forty (64 per cent.) suffered from polyarthralgia. These patients had no joint effusions and the arthralgia settled without sequel. All but three had bilateral enlargement of the hilar glands.

Although the presence of symptoms in the joints in association with erythema nodosum is so well authenticated in the literature, there are no accounts of the actual duration and severity apart from general statements such as that of Löfgren (1953a) that "the symptoms being mild in type generally subside within a couple of weeks".

In James's series the onset of arthralgia preceded the appearance of the skin lesion in 25 of the 62 patients concerned. This precedence, which was first described by Mackenzie (1886), leads such patients to be referred from time to time to rheumatic clinics, and a review of the records over a 10-year period at the Rheumatic Unit of the Northern General Hospital prompted an inquiry into the possible variations in the clinical picture.

Material and Methods

The series consisted of all the patients with erythema nodosum who had been referred to the Rheumatic Unit during a period of 10 years. There were thirty such patients and 23 were reviewed personally. To these were added eleven in whom arthralgia had been an early and prominent symptom but who had been referred to the Respiratory Diseases Unit of the hospital, and four of these were seen personally. The mean duration of follow-up was 4½ years, being less than 1 year in seven cases, from 1 to 5 years in 25 cases, and 6 years or more in nine cases.

Classification of cases according to possible aetiological factors was difficult and patients were therefore divided into two main groups: those with bilateral enlargement of the hilar glands (25) and those without (14). Two patients were not *x*-rayed in the early stages of the disease. These two groups were further subdivided according to whether or not a sore throat had preceded the onset of other symptoms. Eight of the group with hilar gland enlargement, and four of the group without, gave a history of such a preceding infection.

The sensitized sheep cell test was performed by the method of Ball (1950) modified by the use of M.R.C. haemagglutination plates in place of test tubes. Comparison with the results in this laboratory using Ball's original method showed that higher titres were recorded

* Paper read at a meeting of the Heberden Society on December 5, 1959.

on the plates. In order to retain both the specificity and sensitivity of the test it has been considered advisable to designate a titre of 1/128 as the lowest indicating a positive result in rheumatoid arthritis. The results of the sheep cell test in 200 relatives of patients with rheumatoid arthritis (Bremner, Alexander, and Duthie, 1959) were used as controls.

The erythrocyte sedimentation rate (E.S.R.) was measured in venous blood collected in Wintrobe's anticoagulant. Westergren tubes were used and the fall in millimetres was read at the end of one hour.

Results

Age and Sex.—The distribution of patients with regard to age at onset in the two main groups is shown in Fig. 1. The average age of the 25 patients with bilateral hilar gland enlargement was 32 years, only three patients being in the fifth decade. The average age of the second group, those without hilar gland enlargement, was 39, but the variation in age was much greater and extended from 15 to 77 years.

The preponderance of women was striking. There were only five men in the whole series, three being in the group with bilateral hilar gland enlargement.

Involvement of the Joints.—The results of the survey as regards clinical involvement of the joints are summarized in Table I. As might be expected in a rheumatic unit, the joint symptoms preceded the onset of the skin lesions in the majority of cases. In one case the appearance of the skin lesion preceded the onset of arthralgia by 3 days and in five cases they coincided. On the average, however, there was a 2 weeks' interval between the two, the range being up to 7 weeks. The symptoms consisted of pain and stiffness. Morning stiffness was a striking feature in many patients and was a specific complaint in fourteen cases. Abnormal physical signs in the joints consisted of swelling and tenderness (present in 27 cases), and effusion (present in thirteen cases). Involvement of the knees was almost universal, next in order were the ankles, wrists, fingers, shoulders, elbows, and hips.

TABLE I

CLINICAL FEATURES

Length of Time (wks)		Mean	Range
Interval between Onset of Arthralgia and Appearance of Rash		2	0–7
Duration of Arthralgia		26	2–100+
Duration of Rash		3	3 days–6 weeks
Joints Involved (per cent. of cases)	Knees	87	
	Ankles	67	
	Wrists	51	
	Fingers	36	
	Shoulders	36	
	Elbows	26	
	Hips	23	

The duration of the joint symptoms was very variable. In three cases symptoms lasted for only 2 weeks, and in twelve cases they lasted to the end of the follow-up period. In eighteen cases (44 per cent.), symptoms lasted for less than 6 weeks, and in a further twelve for less than 6 months. In eight of the twelve patients who complained of arthralgia at the time of review symptoms had continued on and off throughout the follow-up period. Four of these twelve patients made a good initial recovery, but three had further attacks of erythema nodosum. None of these three showed hilar gland enlargement and sensitivity to streptococci or sulphonamide drugs was the probable cause of the recurrence in two. Amongst the eight patients with persistent symptoms, two had further attacks of erythema nodosum and one of these had a

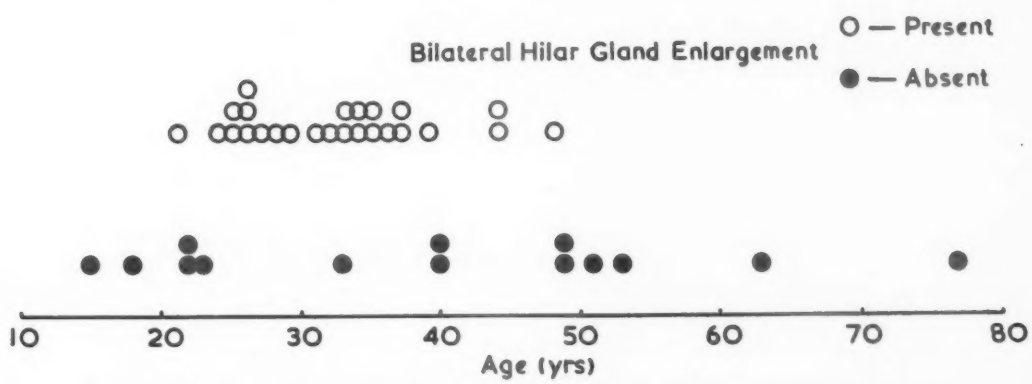

Fig. 1.—Relationship between age at onset and presence or absence of bilateral hilar gland enlargement.

condition clinically and radiologically indistinguishable from rheumatoid arthritis. This patient also had a positive sheep cell test and a review of the history suggested that she was suffering from rheumatoid arthritis in which erythema nodosum had twice occurred as a complication associated with streptococcal or sulphonamide sensitivity. A further patient had evidence of an erosive arthritis, but in this case the sheep cell test was negative and the onset of the arthritis was immediately preceded by the erythema nodosum. Only one of the remaining patients showed radiological abnormalities. This was a woman, now aged 53, who showed changes compatible with a minor degree of generalized osteo-arthritis and in whom this condition may well have been the cause of her persistent joint pain.

An attempt was made to find out whether any features in the early stages of the illness were associated with undue prolongation of joint symptoms. There was some distinction between those patients who had objective signs, such as joint tenderness or swelling, when first seen and those with arthralgia only. Fourteen patients had no objective signs of joint involvement in the early stages, and only two of these continued to have symptoms to the end of the follow-up period. The mean duration of symptoms in the remaining twelve was 5½ weeks. In 27 patients joint swelling or tenderness was present when they were first seen and nine of these had symptoms to the end of the follow-up period. In the remaining eighteen the average duration of symptoms was 11 weeks.

A similar analysis of patients in whom sore throat was an early symptom showed that this also was a factor associated with longer duration of symptoms. Twelve patients had a sore throat initially and, of these, seven still had symptoms at the end of the follow-up period. The mean duration of symptoms in the remaining five was 13 weeks. Sore throat was not a prominent early symptom in 28 patients and, of these, five still had symptoms at the end of the follow-up period. The mean duration of symptoms in the remaining 23 was 8 weeks.

Six patients had more than one attack of erythema nodosum. Five of these had symptoms persisting to the end of the follow-up period and three had signs of joint swelling or tenderness.

The Skin Lesion.—This was in accordance with the classical descriptions and was confined to the lower legs in the majority of cases. In seven patients there were lesions morphologically typical of erythema nodosum on the arms as well as on the legs, and in two further cases there was an additional rash on the body which was classified as erythema multiforme. The skin lesions were present for an average period of 3 weeks, the range being from 3 days to 6 weeks. Some patients showed successive crops of lesions arising during this 6 weeks' period.

Cardiac Involvement.—In eight of the 41 cases cardiac murmurs were heard on first examination, but none was considered to be of pathological significance, all being systolic in timing and usually heard in the pulmonary area. At the time of follow-up only four patients were found to have murmurs, and in three the murmur had been present at the first examination. None was considered to be organic in origin.

Erythrocyte Sedimentation Rate.—The behaviour of the E.S.R. is summarized in Table II. It was high in the early stages, rising to over 60 in fifteen of the 27 cases in which it was recorded initially, and was normal in only one case. The E.S.R. remained raised for a mean period of 16 weeks. In ten cases out of the 27 it fell to normal within 6 weeks. The relation between the duration of raised E.S.R. and duration of symptoms varied. In five patients the E.S.R. remained raised after the symptoms had subsided, and in seven the E.S.R. became normal at the same time as the symptoms disappeared. In one case, however, the E.S.R. remained raised for 10 weeks after the symptoms had subsided, and in fifteen patients the symptoms persisted after the E.S.R. had become normal, in seven of them for more than 6 months.

TABLE II

CHANGES IN CHEST *X* RAYS AND ERYTHROCYTE SEDIMENTATION RATE

Duration of Signs (wks)	Mean	Range	No. of Cases
Bilateral Hilar Enlargement ..	40	8–100	25
Elevation of Erythrocyte Sedimentation Rate	16	<6 7–12 >12	10 8 9
Maximum Erythrocyte Sedimentation Rate (mm./hr Westergren) ..	70	<30 30–60 >60	1 11 15

Radiological Examination.—In 27 patients the hands and feet were *x*-rayed at the time of review. None showed changes such as the circumscribed areas of rarefaction described as typical of sarcoidosis.

Bilateral enlargement of the hilar glands was seen in 25 patients; the duration is summarized in

Table II. The mean duration of hilar gland enlargement was 40 weeks, the range being from 8 to 100 weeks. In nineteen patients the *x* ray had become normal within one year. Thirteen patients also showed radiological evidence of involvement of the lung fields. This consisted for the most part of diffuse mottling. The duration of *x*-ray signs showed no constant relationship to the duration of joint symptoms. In eight cases the *x*-ray signs cleared before the arthralgia ceased and in sixteen cases the arthralgia subsided first. It is worthy of note that none of the patients had persistent *x*-ray changes at the end of the follow-up period. Those who had had involvement of the lung fields did not differ from the rest of the series in regard to duration of joint symptoms or systemic disturbance.

Three patients were considered to have signs of primary tuberculous infection at the time that the erythema nodosum developed. One of these had a further attack of erythema nodosum 4 years later and on that occasion developed bilateral hilar gland enlargement.

Sensitivity to Tuberculin.—The sensitivity to intradermal injection of tuberculin was determined in twenty cases. The reaction was positive at a dilution of 1/1,000 in five cases, and at a dilution of 1/100 in nine cases. The remaining six cases failed to react. Eighteen of the patients whose sensitivity to tuberculin was determined were amongst the group with bilateral enlargement of the hilar glands and only five of these failed to react to a dilution of at least 1/100.

Sensitized Sheep Cell Test.—This test was performed on 22 patients at the time of review. The results of the test are illustrated in Fig. 2, where they are compared with those obtained from 200 relatives of patients with rheumatoid arthritis. Twelve of the erythema nodosum patients show a titre of 1/32 or higher compared with eighteen of the 200 controls. There is no relation between these titres

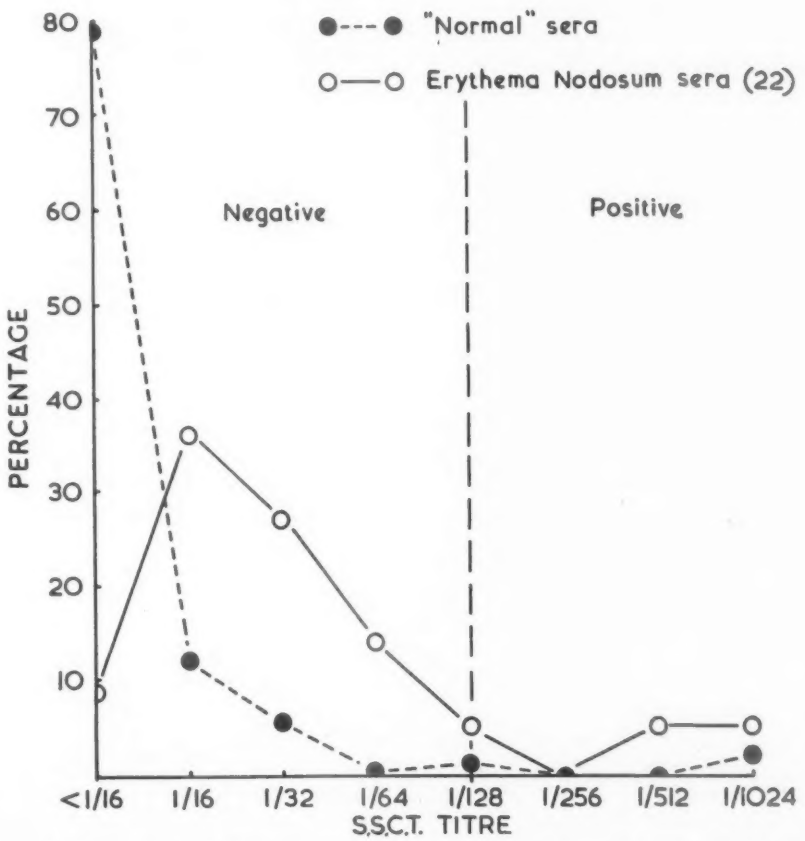

Fig. 2.—Results of sensitized sheep cell test (S.S.C.T.) compared with the results in a "normal" series of 200 relatives of patients with rheumatoid arthritis.

and such factors as duration of symptoms, duration of raised E.S.R., or presumed aetiological factors. The difference between the two groups at the level stated is highly significant ($\chi^2_c = 27 \cdot 68$), but in view of the small numbers no importance can be attached to the shape of the curve.

Treatment.—During the acute stage of the illness this consisted of rest in bed and aspirin by mouth in a dose of 60 to 80 gr. a day. Five cases were treated with steroid hormones in the early stages for periods up to a maximum of 6 weeks. In each of these there was a rapid regression of the skin lesion and the temperature became normal. There is no evidence to suggest that the subsequent clinical course of these patients differed from that of the rest of the series.

Discussion

A study of the symptoms and signs in these 41 patients reveals a clinical syndrome of fairly uniform pattern, particularly with regard to involvement of the joints. Certain variations within this pattern are worthy of note. In patients with bilateral enlargement of the hilar glands the age at onset was lower than in the remainder, being mainly confined to the third and fourth decades, but the two groups did not differ significantly in other respects. Precise aetiological classification was difficult, but the results suggest a relationship between erythema nodosum and joint manifestations which is independent of possible aetiological factors such as drug-sensitivity or streptococcal or tuberculous infection. In three patients, in which a diagnosis of primary tuberculosis was made, the clinical picture differed in no particular respect from that seen in the remainder of the series. In those patients in whom sore throat was an early manifestation, or in whom objective signs in the joints were observed, the disease tended to run a more protracted course, irrespective of whether the hilar glands were enlarged or not.

The predominance of women in the series was striking. This conforms with the observation of James (1959), who found that 70 per cent. of his cases of sarcoidosis with erythema nodosum were women, whereas the sex incidence of sarcoidosis as a whole was more equal.

The systemic disturbance, usually marked at the onset, quickly subsided in the majority of cases, and in two-thirds the E.S.R. had returned to normal within 4 months. The absence of serious pulmonary involvement was worthy of note. In this respect there may be some difference between patients with bilateral hilar gland enlargement and erythema nodosum and a similar group of patients without erythema nodosum who might be classified as cases of sarcoidosis on the grounds of low sensitivity to tuberculin and histological evidence of a sarcoid type of reaction. Löfgren (1953b), in his study of 212 patients with bilateral enlargement of the hilar glands, found a tendency to persistence of pulmonary lesions in only 8 per cent. of cases with erythema nodosum compared with 28 per cent. of cases discovered on routine *x*-ray examination or on investigation of symptoms other than those of erythema nodosum. However, he considered that the difference might be due to earlier diagnosis in the case of the patients with erythema nodosum. Scadding (1956), in a series of 102 cases of sarcoidosis, found that a good prognosis could be given to those patients who first came under observation with enlarged hilar lymph nodes only. In the present series no patient showed clinical evidence of rheumatic heart disease, and none developed active pulmonary tuberculosis.

From the point of view of joint involvement, there was again no significant difference between the patients with bilateral hilar gland involvement and those without.

No crippling form of arthritis developed, even amongst those patients with prolonged signs. Two patients, however, did show an erosive arthritis, mainly affecting the hands, but one of these may have been a case of rheumatoid arthritis in whom erythema nodosum occurred as an incidental complication. In this case the erythema nodosum was associated with an exacerbation of joint symptoms. Among the remaining ten patients with prolonged symptoms, only five had actual joint swelling or tenderness and this was relatively mild, only one or two joints being involved, though the symptoms were sufficiently troublesome for them to continue taking moderate doses of aspirin.

The results of this study indicate that the prognosis in patients presenting with erythema nodosum and arthralgia, with or without bilateral hilar gland enlargement, is excellent, although joint symptoms may persist in some for many months, especially if sore throat precedes the onset. There is no evidence to support the view that rheumatic fever, tuberculosis, or progressive sarcoidosis occur commonly amongst these patients. Thus treatment should be on simple conservative lines. Rest in bed need not be unduly prolonged. Adequate doses of aspirin will suffice to control symptoms in the majority of cases and steroids are rarely indicated. Treatment in the form of prophylactic penicillin or anti-tuberculous drugs will be required only in rare instances with unequivocal evidence of rheumatic carditis or active tuberculosis.

Summary

(1) 41 patients with erythema nodosum in whom arthralgia was an early and prominent symptom have been followed for an average period of 4½ years. The clinical course of these patients is described with particular reference to signs and symptoms affecting the joints.

(2) The condition was essentially benign, although joint symptoms persisted in some patients for many months. These were particularly liable to persist where sore throat was an early symptom, where swelling or effusion was noted in the early stages, or where erythema nodosum was recurrent.

(3) No evidence was seen in this series to support the idea that rheumatic fever, tuberculosis, or progressive sarcoidosis occur commonly among these patients.

(4) The results of the sensitized sheep cell test (S.S.C.T.) performed at the time of review, showed agglutination at higher titres within the sero-negative range than the results in a control group.

It is a pleasure to acknowledge the help and advice given me by Dr. J. J. R. Duthie during the course of this survey. I should also like to thank my colleagues of the Respiratory Diseases Unit for permission to see their cases and, in particular, Dr. A. C. Douglas for his help.

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Manifestations articulaires de l'érythème noueux

RÉSUMÉ

(1) On a suivi l'évolution clinique de 41 malades atteints d'érythème noueux, chez qui l'arthralgie avait été un symptôme précoce et proéminent, pendant une période de 4 ans et demi en moyenne. On décrit l'évolution clinique de ces malades, avec référence particulière aux signes et symptômes articulaires.

(2) L'affection fut essentiellement benigne, bien que les symptômes articulaires aient persisté chez quelques malades pendant plusieurs mois. Cette tendance à la persistance de la symptomatologie articulaire fut notée particulièrement chez ceux qui avaient débuté par une angine, par une tuméfaction ou un épanchement, ou chez ceux dont l'érythème noueux fut récurrent.

(3) Dans cette série on ne trouva rien à l'appui de la théorie que le rhumatisme articulaire aigu, la tuberculose ou la sarcoïdose progressive surviennent souvent chez ces malades.

(4) Des réactions avec des globules de mouton sensibilisées, effectuées durant une revue des malades, accusèrent des agglutinations à des titres supérieurs, en dedans des limites séro-négatives, que ceux des témoins.

Manifestaciones articulares del eritema nudoso

SUMARIO

(1) Se siguió el curso clínico de 41 enfermos con eritema nudoso, en los cuales la artralgia fué un síntoma precoz y destacado, durante un período medio de tiempo de 4 años y medio. Es descrita la evolución clínica de estos enfermos con especial referencia a los síntomas y signos articulares.

(2) La afección fué esencialmente benigna, aunque los síntomas articulares persistieron en algunos enfermos durante muchos meses. Fueron particularmente propensos a esta persistencia de la sintomatología articular aquellos casos en que una angina fué un síntoma precoz, o en que una hinchazón o un derrame aparecierón en los estadios iniciales, o finalmente en que el eritema nudoso fué recurrente.

(3) En esta serie no apareció ningún dato que justifique la idea de que el reumatismo poliarticular agudo, la tuberculosis o la sarcoidosis progresiva afecten con frecuencia a estos enfermos.

(4) Las reacciones con glóbulos de carnero sensibilizados, efectuadas durante la revisión de los enfermos, acusaron aglutinaciones a títulos mayores, dentro de la norma sero-negativa, que en los testigos.

DISCUSSION

DR. B. ANSELL (*Taplow*) asked whether any second attacks of erythema nodosum were again associated with arthritis.

PROF. S. J. HARTFALL (*Leeds*) asked whether any antistreptolysin titres were carried out.

DR. J. S. LAWRENCE (*Manchester*) asked whether the seasonal incidence was significant.

DR. A. ST. J. DIXON (*London*) said he was glad to hear that attention had been drawn to the fact that the arthralgia of erythema nodosum sometimes remained after all objective signs had disappeared, because some patients had been labelled psychoneurotic because of this complaint. He asked whether any observations had been made of "T"-wave changes in the electrocardiograms. He said that these had been reported as part of the syndrome and had in the past caused confusion with rheumatic carditis.

DR. A. G. S. HILL (*Stoke Mandeville*) said that Dr. Wilkinson at Stoke Mandeville had found positive sheep cell tests in a small proportion of patients; these subsequently became negative as the condition subsided. In this condition he had noticed a period of 2 or 3 weeks of general malaise before anything else happened. This caused a diagnostic problem. He wondered whether the polyarthralgia was ever seen without erythema nodosum, and whether this was one of the benign polyarthritides.

PROF. E. G. L. BYWATERS (*London*) said that they saw a fair amount in children at Taplow and in adults at Hammersmith. In general it seemed that the joint

manifestations were much more common in adults and less common in children. He did not know whether any information existed on the histological appearances. It had been thought that the occasional abdominal pain or joint manifestations might be panniculitis occurring in deep spots, similar to panniculitis in superficial areas. There was a widespread feeling that erythema nodosum and joint pain entailed an association with rheumatic fever. He had seen only one case in which there was rheumatic carditis. Finally, he asked what the speaker's regime of treatment was, particularly in cases with a positive Mantoux.

DR. TRUELOVE replied that second attacks were observed in four patients, and that all four had persisted with signs at the end of the follow-up, two of them having had three attacks. Antistreptolysin titres were not done, and the seasonal incidence had not been worked out. Nor had electrocardiograms been done routinely, so that he could give no information about "T"-wave changes.

In reference to sheep cell titres, he emphasized that the sheep cell tests shown had been done at the end of the follow-up period. He had no conclusive information on what the titres were at the beginning, although he had seen positive readings in a number of patients. He had the impression that these patients did not need specific treatment, except rest in bed and salicylates, but in patients treated with steroids the erythema nodosum had subsided more quickly than in the others. Steroids were given only for short periods up to 6 weeks, and there did not appear to be much distinction between those treated with steroids and those without.

PROF. E. G. L. BYWATERS (*London*) asked if PAS or INAH had been used.

DR. TRUELOVE replied that these drugs were given to patients with bilateral hilar gland enlargement.

DR. J. J. R. DUTHIE (*Edinburgh*) said that they had wondered whether if steroids were given to patients with sarcoidosis they should be "covered" with antibiotics, but that their colleagues, the chest physicians, had assured them that this was no longer necessary.

PROF. E. G. L. BYWATERS (*London*) said that it was sometimes difficult to know whether a patient had sarcoidosis or tuberculosis. There were Mantoux-positive cases of sarcoidosis and sometimes Mantoux-negative tuberculosis patients, at least for a while. He thought the question of giving antibiotics was very important, and felt that cortisone should not be given to any great extent to such patients without "covering" it with suitable antibiotics.

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EMPIRE RHEUMATISM COUNCIL

TWENTY-THIRD ANNUAL REPORT*

The 23rd Annual Report of the Empire Rheumatism Council was presented by the Chairman, Dr. W. S. C. Copeman, at the Annual Meeting held on May 3, 1960, at St. James's Palace. The President, H.R.H. the Duke of Gloucester, was in the chair.

Dr. Copeman introduced his report by announcing that over £56,000 had been devoted to research in 1959 as against £4,600 in 1951.

The projects being financed covered a very wide field, including laboratory research into the basic problems of the rheumatic diseases in many universities and hospitals throughout the British Isles and in the Commonwealth, survey work in industry, in town and country, and the setting up of new Units in order that new projects might be undertaken.

They were all very grateful to those whose generosity had made possible the advances of the past 10 years, and special mention was made of the Geigy Pharmaceutical Company who established the Geigy Travelling Fellowships in 1953, which had allowed British research workers to exchange knowledge with those working overseas. The Company had now renewed their donation under Deed of Covenant which would, by contributing £23,000 during the next 7 years, allow these valuable fellowships to continue.

Research

Electron Microscopy Unit.—The first unit of its kind in the world had been established by the Council at St. Thomas's Hospital Medical School, London. The Director of the Unit, Prof. D. V. Davies, Professor of Anatomy at the Medical School, would carry out research into the cartilage and other tissues having a direct bearing upon osteo-arthritis. The cost to the Council of this installation was between £12,000 and £15,000.

Industrial Rheumatism Unit.—The Council had decided to establish a special Unit to make a comprehensive study of the social and economic effects of rheumatic diseases in British industry. It would be under the direction of Dr. J. J. R. Duthie of Edinburgh University, and among its objectives would be:

> To gain accurate information of the prevalence of the rheumatic diseases in specific industries.
>
> To estimate the financial implications.
>
> To investigate working conditions that may cause rheumatism and examine industrial processes with a view to advising how this might be reduced.
>
> To designate occupations suitable for workers disabled by rheumatism and arthritis.

In a report upon this subject, Dr. Duthie points out that among the employed population of Great Britain more than 730,000 persons claim sickness benefit by reason of rheumatism each year, leading to a loss of more than 27 million working days. It has been shown, on the basis of a detailed examination in several industries in the U.S.A., that although the cost of sickness benefit to the operative is high, the cost to the employer is four times as great.

The study of the geographical distribution of rheumatism showed that over 80 per cent. of cases were located in the industrial areas, providing a strong indication that occupational influences may be of greater importance than climatic variations.

The more serious forms of rheumatism and arthritis rendered sufferers incapable of pursuing their former occupations. The existing services provided only a limited solution to the problem of resettling such patients. It was expected that this investigation would cost the Council about £6,000 a year at the outset.

Survey Revelations.—Although so many people suffered from arthritis and other forms of rheumatism there were no exact statistics available about its incidence until the Council set up its Mobile Field Survey Unit, the only one of its kind in the world.

The surveys carried out by this Unit under its Director, Dr. J. S. Lawrence, had yielded a number of interesting revelations. It was now clear that about one person in twenty in Great Britain suffered at one time or another from an acute form of rheumatism (polyarthritis). This could be severe, confining the sufferer to bed, but unlike rheumatoid arthritis it often disappeared and was not followed by permanent arthritis or heart disease. The survey indicated that such attacks mostly occurred towards the end of the winter, about February and March, and might be the result of some bacterial or virus infection. It was important that this temporary condition should be distinguished from the more serious and crippling forms of arthritis.

These surveys had also shown that the most common complaint among male manual workers was disk

* Full details of the activities of the Council for the year 1958-59 are given in the Report which may be obtained from the Secretary, Mr. M. C. G. Andrews, Faraday House, 8 Charing Cross Road, London, W.C.2.

degeneration of the spine. Further analysis had shown that certain disk complaints were connected with rheumatoid disease, and it was therefore important to distinguish cases in which rheumatoid disease was present to ensure that correct treatment was given.

Research in Birmingham.—A new project undertaken in the University of Birmingham under Prof. J. R. Squire dealt with the rheumatoid factor and its purification. Its importance had been recognized by industrialists and others in that City, and on the initiative of Mr. Ag. Norton and Mr. Marston Riley the sum of £200,000 had now been raised. This would allow accommodation and sufficient funds to be provided for the full project to be undertaken, and the Council would like to express its appreciation to all those who had made this possible.

The Aspirin Riddle.—Salicylic acid was known to have been employed by Hippocrates about 2,500 years ago, mainly for the reduction of fever. The early herbalists in Britain extracted it from the bark of the willow-tree and used it for several complaints. After 1875 it was produced artificially in form of aspirin and had since become the medicine most commonly used in all forms of rheumatism. Yet despite years of research its method of action was still unknown.

One important step towards the understanding of the effect of aspirin had resulted from work done at King's College Hospital, London, by Dr. V. Moses, the Council's Wyeth Fellow in Pharmacology, who had shown that the chemical action of aspirin had an effect upon the carbohydrates and proteins in the body. Since aspirin often had to be taken for long periods its effect was being studied with the aid of radio isotopes.

At the London Hospital Dr. J. A. Hicklin had been measuring the amount of potassium and energy lost by certain tissues of the body when salicylates were taken.

At University College, Mr. R. J. Ladd, as the result of injecting dissolved aspirin into the blood stream, had obtained evidence suggesting that the drug alters the size of the blood vessels; it appears that it reduces the size of dilated blood vessels, but dilates those which are constricted. Changes of temperature were also shown to exert a definite influence, and in order to carry this inquiry further a special machine has been constructed to measure the flow of blood to the hand, and to control changes of temperature accurately.

Education

The Council continued to regard its educational activities as second only in importance to research. The periodic "Reports on Rheumatic Disease", which were started in 1958 for the general information of medical practitioners, had been continued. It was significant that over 1,000 requests had been received for folders in which these reports could be filed, suggesting that they had been found of specific value. Other activities had included the issue of a third handbook (on rheumatic fever), the preparation of a fourth, on gout, a record card for patients undergoing steroid treatment of which 40,000 had been issued and which might be taken over by the Ministry of Health, exhibition material, etc. In addition, the Council had run a number of high-level symposia for consultants and scientists.

Commonwealth

A special section was included in the Report setting out the relationships of the Council with the different Commonwealth countries and how these had been developed in recent years. Important activities had been stimulated in Canada, Australia, and New Zealand, and friendly liaison had been established with the organization and development of research.

The chairman recorded with regret the recent death of the first Secretary to the Council, Sir Frank Fox, O.B.E., at the age of 85 years. Sir Frank had organized the setting up of the Council in 1936, and had guided its affairs during the first difficult years and for the duration of the War. He retired in 1948 and died at West Wittering where he lived in his retirement. On behalf of all members of the Council he expressed condolences to his family.

Of the present Secretary, Mr. M. C. G. Andrews, he could not speak too highly. It must be obvious to all that if he were not so efficient, hardworking, and far-seeing the Council would not hold its increasingly important position. He was ably assisted by Brigadier D. J. B. Houchin and the loyal and efficient office staff, headed by Mrs. V. Brown. A regional representative, Mr. A. Wilton Steer, had recently started work in the Leeds and N.E. England area.

Finally he thanked the Honorary Medical Officers and members of the working committees of the Council, whose names were to be found in the Report. Although many of them had to travel long distances, the record of attendance at meetings was higher than that of any other body of which he had experience.

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HEBERDEN SOCIETY

Clinical Meeting.—At a meeting held at the West London Hospital on February 26, 1960, the president, Dr. F. Dudley Hart, was in the chair, and the following papers were presented:

Results of Long-term Treatment of Rheumatoid Arthritis with Corticotrophin. DR. P. S. DAVIS (*West London Hospital*): Daily subcutaneous injections of corticotrophin gel were given to forty patients, all of whom were suffering from severe, active rheumatoid arthritis and had not improved with rest in hospital, salicylates, and (in the majority of cases) gold or phenylbutazone, and they were followed up for a minimum of 2 years. Treatment had been discontinued in six patients because of side-effects and in seven because of acquired resistance, and complete remissions in a further six patients had allowed treatments to be stopped before the conclusion of the 2-year assessment. Dosage was adjusted according to the clinical response, and the total 17-hydroxycorticosteroid output was watched in order to avoid over-stimulation of the adrenals and to minimize side-effects.

The results of treatment on the strength of grip, erythrocyte sedimentation rate, and radiological appearances were at least as good as those obtained with prednisolone according to the published results of the Medical Research Council/Nuffield Foundation Prednisolone-Analgesic Trial (*Ann. rheum. Dis.*, 1959, **18**, 173). Preliminary results also indicated that corticotrophin gel caused a fall in the titre of the Rose-Waaler test in an appreciable number of patients, in contrast to the tendency of the titre to rise with prednisolone therapy. The relative ease of withdrawal of therapy when necessary was another factor in favour of corticotrophin gel.

Discussion.—THE PRESIDENT asked whether there were any septic or allergic reactions.

DR. DAVIS replied that they had had none since they went over to subcutaneous injections, and only two or three in patients receiving the original intra-muscular injections. One or two cases of allergy associated with resistance to corticotrophin subsequently responded to increased dosage.

DR. G. R. NEWNES (*Sheffield*) said that their experience in Sheffield corresponded very closely with that of Dr. Davis. They felt convinced that corticotrophin was the treatment of choice for the severe rheumatoid arthritic. It was more physiological than treatment with steroids and, provided the dosage was controlled carefully, and the patient very quickly learnt to help with the control of dosage, the complications and side-effects were very much less. They felt that there was evidence that corticotrophin could be given for prolonged periods. They had met the difficulty of acquired resistance to corticotrophin, and that was something to be overcome. During the past 8 years, in many thousands of injections, they had had only one abscess, which was due to an intramuscular injection.

DR. A. ST. J. DIXON (*London*) said that these results were encouraging, but before accepting them entirely there were one or two points he would like to clear up. He wondered if the improvement in the sheep-cell titre could be due to improvement in the test? He asked if there were any deaths in the series, and whether they had compared their *x* rays with those of the M.R.C. series.

DR. DAVIS replied that they could exclude improvement in the test because the patients transferred from corticotrophin to steroids then showed a rising titre, in the same year. They had not had an opportunity of seeing the *x* rays of the M.R.C. trial, but their own *x* rays were read without knowledge of what each patient was receiving. They had had one death from diffuse intestinal bleeding, in a patient who was overstimulated with corticotrophin.

DR. J. SHARP (*Manchester*) asked for further information about acquired resistance.

DR. DAVIS replied that that was a very complex problem. They had found that in some patients the resistance was a temporary phenomenon. If the dosage were increased or injections given twice daily the adrenals might respond. In one striking case, a young woman, after an initial good response, became resistant and needed 80 units daily. Then, some months later she became responsive again and the dosage could be cut to 10 units daily. They had sometimes had to increase the dosage to 80 units twice daily to obtain a response.

THE PRESIDENT asked whether this involved the same batch of ACTH gel.

DR. DAVIS replied that the problem of batch variation was largely a thing of the past.

DR. G. D. KERSLEY (*Bath*) asked whether anybody was working with a combination of ACTH and steroids. He had used them together in several difficult cases with benefit, but he wondered whether stimulation once or twice a week in a patient on steroids would be beneficial if the patient had an accident or any sudden stress.

DR. DAVIS said that it had been shown that stimulation with corticotrophin did not protect the patient on ordinary oral steroids, as it was pituitary suppression that resulted from corticosteroids. Why the patient did not have a withdrawal syndrome when corticotrophin was stopped was far from clear. He thought one important factor was the way in which the drug was given once daily. There was only intermittent adrenal stimulation for about 16 hours in the day.

DR. W. A. BOURNE (*Hove*) asked whether they had made any observations on the effects on the spine during treatment.

DR. DAVIS said that osteoporosis was the same as with oral corticosteroids. In the entire series they had seen only about 4 per cent. in the 8 years.

Generalized Rheumatism in Temporal Arteritis. DR. G. PARSONS SMITH (*West London Hospital*): A review of the clinical and pathological features of temporal arteritis, with representative cases shows that, although the lesions occur principally in the carotid and vertebral arteries, with especial threat to vision, the characteristic giant cell arteritis has been found in the larger arteries to the limbs and viscera. Among the presenting symptoms of the disease, diffuse muscle and joint pains are not uncommon, and severe, localized, muscular pain may occur during an acute episode. Corticotrophin therapy was of some value, especially when ocular symptoms called for urgent treatment to save vision.

Heberden (1816) mentioned, among cures for headache, the opening of a temporal artery, an operation which is now most effective in relieving the local pain. The rheumatic symptoms are immediately controlled with 5 mg. prednisolone thrice daily, but in those patients in whom vision fails intravenous corticotrophin should be given as soon as possible.

REFERENCES

Heberden, W. (1816). "Commentaries on the History and Cure of Diseases", 4th ed. London.
Parsons Smith, G. (1959). *Brit. J. Ophthal.*, **43**, 204.

Discussion.—DR. M. S. GOOD (*Aylesbury*) asked whether heparin had been used in many cases. The pathology was in some doubt and it was difficult to know how much was due to thrombosis and how much to arteritis. He agreed with the speaker's views on the use of steroids. He had had a personal communication from Dr. G. A. K. Missen who had examined seventeen cases which had come to *post mortem*; in this series the circle of Willis had not been affected, but mainly the vertebral and, to a lesser degree, the meningeal arteries.

DR. PARSONS SMITH replied that he had used heparin, occasionally. The posterior cerebral artery could be involved as in the case described by Crompton.

THE PRESIDENT said that on the reported findings early steroid therapy was justified in prevention of the ocular features. He had been disappointed in one or two cases, but he had probably started too late and given too little.

DR. PARSONS SMITH replied that he would recommend the use of corticotrophin for every elderly person who suddenly lost the sight of an eye. It could do no harm and might be the means of saving sight. He gave ACTH for one month and apart from a few rheumatic pains there were no residua.

THE PRESIDENT said that there was occasionally a residual raised erythrocyte sedimentation rate for some weeks or months, which suggested that the inflammation was not completely suppressed.

DR. W. A. BOURNE (*Hove*) said that he agreed with starting steroids at an early date. In one case in which the diagnosis had been made he had waited for 24 hours to obtain the result of a biopsy and the patient had lost his sight in that time. Another patient had lost his sight and developed a monoplegia.

DR. G. D. KERSLEY (*Bath*) asked what dosage of corticotrophin had been given.

DR. PARSONS SMITH said that he gave 20 units intravenously the first day and 20 units the second day; then 50 units intramuscularly for 2 days, and 20 units intramuscularly twice daily for a month.

DR. M. S. GOOD (*Aylesbury*) said that, of the twenty personal cases he had seen, twelve had eye signs and symptoms, and in these corticosteroids were essential. The question whether one should start the treatment in patients who were merely suffering from headaches before biopsy confirmation of the disease was a more difficult one. He did not think that those patients should be given ACTH straightaway. It was only rarely that the eye symptoms were early and so dramatic as in the case demonstrated by Dr. Parsons Smith.

THE PRESIDENT: "How rare?"

DR. M. S. GOOD: "About 1 per cent."

THE PRESIDENT: "I thought it was more than that."

DR. PARSONS SMITH: "The world literature gives 25 per cent."

DR. GOOD: "As presenting symptoms of blindness, only about 1 per cent."

THE PRESIDENT: "You mean temporal arteritis with acute ocular involvement, do you not?"

CLINICAL PRESENTATIONS

Arthrodesis of the Wrist in Rheumatoid Arthritis. MR. J. C. F. HINDENACH (*West London Hospital*) showed cases and described the indications, technique, and results of arthrodesis of the radiocarpal joints in rheumatoid arthritis. The beneficial effects were discussed, especially in terms of subsequent hand function, and it was stressed that no surgical hazards had resulted from concurrent corticotrophin therapy in these patients.

DR. J. H. BARON (*The Middlesex Hospital*) described two cases of Reiter's syndrome complicated by spondylitis and aortitis with aortic value incompetence. The first patient, a woman aged 29, had been shown at a clinical meeting of the Society in 1950 by Dr. F. Dudley Hart, and the progressive features of the illness were listed and necropsy findings presented.

DR. G. BROWN (*Westminster Hospital*) presented the case history of a man suffering from classical ankylosing spondylitis complicated by iritis and aortic incompetence.

Side-Effects of Oral Corticosteroid Therapy in Adult Rheumatoid Arthritis. DR. OSWALD SAVAGE (*West London Hospital*): The third M.R.C./Nuffield Steroid Trial* showed that patients on prednisolone maintained a significant advantage over those on aspirin or other analgesics throughout a 2-year period. In addition repeated radiological examination demonstrated that the progression of joint damage was less marked in the prednisolone-treated group and that, if the dose was kept below 15 mg. daily, serious side-effects were relatively uncommon. Because of this the relative incidence of side-effects assumes increasing importance.

Figures of incidence were collected from eight centres, totalling 910 cases. The most common was rounding of the face in women, but this rarely necessitated withdrawal of the treatment. Dyspepsia was common (32 per cent.) and although peptic ulceration (10 per

* *Ann. rheum. Dis.*, (1959) **18**, 173.

cent.) was infrequent, most of the ulcers gave rise to complications. A series of 104 cases from the West London Hospital was compared with the eight-centre survey. Dyspepsia was higher (47 per cent.); of cases of dyspepsia 43 per cent. were mild and transient, 34 per cent. moderate with a negative barium meal, and 23 per cent. (11 of the 104 cases) had proven ulcers. The average dose in the cases developing ulcers was 25 mg. prednisolone per day. In the cases of dyspepsia with negative radiology the average dose differed little from those without indigestion. The importance of aspirin in addition to steroids in producing dyspepsia was discussed.

There seemed to be no doubt that, in conditions such as ulcerative colitis and asthma, where long-term steroid therapy was used without the addition of aspirin, dyspepsia was uncommon. Hypertension was quite common (13 per cent.), but very rarely necessitated withdrawal of steroids.

Other side-effects (such as fractures, peripheral neuritis, bruising, and mental changes) were under 5 per cent. It was concluded that in order to reduce the incidence of side-effects it was imperative to keep the dose below 15 mg. prednisolone per day, and to recognize that other drugs such as aspirin might play a part in their production.

When dyspepsia occurred with long-term steroid therapy aspirin should be withdrawn and replaced with enteric-coated salicylates.

Discussion.—DR. A. ST. J. DIXON (*London*) said that he had found no difference in faecal blood loss between patients on steroids and aspirin and on aspirin alone, during tests lasting a week or so. But one should avoid giving the two together, as rheumatoid patients receiving both aspirin and corticosteroids for long periods developed serious intestinal complications more frequently than patients suffering from skin diseases or ulcerative colitis who were given corticosteroids without aspirin.

DR. A. G. S. HILL (*Aylesbury*) said that sixty patients treated with a daily dose of 5 mg. prednisolone, the incidence of dyspepsia was 10 per cent., but it had been sufficiently severe to stop treatment in only two patients. Purpura was common and had been detected in 20 per cent. There was one case of peri-colic abscess and one of melaena.

THE PRESIDENT asked whether the bruising occurred only in females.

DR. A. G. S. HILL (*Aylesbury*) replied that it was almost always in females.

DR. SAVAGE said that he agreed. He had never seen bruising in a male patient receiving steroids.

DR. G. D. KERSLEY (*Bath*) asked how far this was a controlled series. Quite a lot of women bruised without prednisolone, but 20 per cent. was a high figure. He asked if these were big patches of skin bruising.

DR. A. G. S. HILL (*Aylesbury*) replied that the observations were completely uncontrolled, and that all the bruises were as big as sixpences or bigger.

Alteration in Programme for 1960

The Heberden Round will be conducted by Dr. W. S. Tegner at the London Hospital on September 16, 1960, and not on September 23 as previously announced.

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BRAZIL

Rheumatological Society of Rio de Janeiro

This new branch of the Brazilian Society of Rheumatology has recently been formed. The following officers have been elected:

President:	Dr. Jacques Houli.
Vice-Presidents:	Dr. Nelson Senise.
	Dr. Caio Villela Nunes.
Secretary:	Dr. Israel Bonomo.
Executive Committee:	Dr. Ideal Peres.
	Dr. R. E. Araujo Leitão.
	Dr. Waldemar Werttreich.
Treasurers:	Dr. Berel Bejgler.
	Dr. Odir Mendes Pereira.
Librarian:	Dr. Jacob Gamarski.

New Chair of Rheumatology

Dr. Pedro Nava has been appointed to the Chair of Rheumatology which has been created in the Catholic University of Rio de Janeiro, Brazil. His undergraduate and postgraduate teaching courses will start this year.

W.S.C.C.

GREECE

The Rheumatic Diseases and their Treatment. By G. Spanopoulos. 1958. Pp. 175, figs. Athens.

Dr. George Spanopoulos is the author of the first well-documented book on the rheumatic diseases to be published in the Greek language. He uses the British classification and many of his references are to English work in this field.

He has also recently published a small book entitled "The importance of the sensitized sheep-cell agglutination test in the diagnosis of the rheumatic diseases and the prognosis of rheumatoid arthritis". W.S.C.C.

NEW YORK RHEUMATISM ASSOCIATION

Officers, 1960-61

At the Annual Meeting of the New York Rheumatism Association, held on April 19, 1960, at New York University-Bellevue Medical Center, the following officers were elected:

President:	Dr. Ronald W. Lamont-Havers.
Vice-President:	Dr. Sidney S. Berkowitz.
Secretary-Treasurer:	Dr. Albert W. Grokoest.

SOCIETÁ ITALIANA DI REUMATOLOGIA

Seventh Rome Rheumatology Day, 1960

A successful meeting, remarkable both for the excellence of the papers given and the large number of persons attending, was organized by Prof. T. Lucherini, Prof. C. Cervini (*Secretary*), Dr. A. Ciocci, and Dr. C. Longo, on March 19 and 20, 1960.

Among the principal contributors were the following:

Prof. A. Fieschi and Prof. V. Bianchi (*Institute of Medical Pathology of the University of Genoa*): "Raynaud's Phenomenon and Scleroderma."

Prof. C. B. Ballabio and Prof. G. Grampa (*Milan*): "Clinical Deterioration and Collagen Pathology in Patients Treated with Cortisone."

A symposium on the Immunology of the Rheumatic Diseases was conducted by Prof. L. Michelazzi (*Genoa*), Prof. C. Cavallero (*Pavia*), Prof. G. Della Pietra (*Naples*), Prof. V. Carcassi (*Siena*), Prof. L. Bonomo (*Bari*), and Prof. A. Marmont.

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ABSTRACTS

This section of the ANNALS *is published in collaboration with the two abstracting Journals,* ABSTRACTS OF WORLD MEDICINE, *and* OPHTHALMIC LITERATURE, *published by the British Medical Association.*

The abstracts selected for this Journal are divided into the following sections: Acute Rheumatism; Chronic Articular Rheumatism (Rheumatoid Arthritis, Osteo-Arthritis, Spondylitis, Miscellaneous); Disk Syndrome; Gout; Pararheumatic (Collagen) Diseases; Non-Articular Rheumatism; General Pathology; ACTH, Cortisone, and other Steroids; Other General Subjects. At the end of each section is a list of titles of articles noted but not abstracted. Not all sections may be represented in any one issue.

The section "ACTH, Cortisone, and other Steroids" includes abstracts and titles of articles dealing with research into the scope and modus operandi *of steroid therapy.*

Acute Rheumatism

Relation of Duration of Bed Rest in Acute Rheumatic Fever to Heart Disease Present 2 to 14 Years Later. LENDRUM, B. L., SIMON, A. J., and MACK, I. (1959). *Pediatrics*, **24**, 389. 4 refs.

An analysis is presented of the long-term results of the treatment of children with rheumatic fever without prolonged rest in bed. Of 360 patients followed up for more than 2 years after discharge from Herrick House, Bartlett, Illinois, 269 had been admitted immediately clinical evidence of acute rheumatic fever had disappeared. As soon as temperature, sleeping pulse rate, leucocyte count, and erythrocyte sedimentation rate approached normal, increasing activity was allowed. The average stay at the home was 3 months. The remaining 91 patients, who served as controls, had been admitted after prolonged periods of rest in bed. The cardiac status at the follow-up examination was assessed on the basis of significant changes in heart murmurs, change in size of the heart as seen radiologically, and changes in blood pressure indicating aortic incompetence. Assessment of the adequacy of medical care in both groups, including prophylaxis against streptococcal infection after discharge, showed that this care was slightly better in the control group.

Of the 269 patients in the experimental group 169 were followed up for 2 to 4 years, 97 for 5 to 9 years, and three for 10 years or longer. In the control group 28 were followed up for 2 to 4 years, 57 for 5 to 9 years, and six for 10 years or longer. At the time of the final follow-up examination 62 (26 per cent.) of the experimental group were worse compared with 37 (41 per cent.) of the control group. When patients who had a recurrence (subacute bacterial endocarditis or "chronic myocarditis") were excluded, 21 (12 per cent.) of the experimental group and thirteen (25 per cent.) of the controls were worse. Of 100 patients in the experimental group followed up for more than 5 years, sixteen were better, 51 were unchanged, and 33 were worse, whereas of the 63 controls, nine (14 per cent.) were better, 25 (40 per cent.) were unchanged, and 29 (46 per cent.) were worse. Although the numbers are relatively small, it is considered that they lend support to the view that prolonged rest in bed after an acute attack of rheumatic fever is "not necessary for optimal healing of the injured heart".

C. Bruce Perry.

Treatment of Chorea with Corticosteroid Hormones. [In Russian.] RYNSKAJA, L. M. (1959). *Klin. Med.* (*Mosk.*), **37**, 62. 26 refs.

The danger of valvular disease and heart failure resulting from chorea is particularly great in pregnant women; according to Wilson and Price the maternal mortality is 33 per cent. and the infant mortality 50 per cent. The treatment of chorea with corticosteroids, which has been reported by various authors to have a rapid and beneficial effect, is therefore logical and justifiable.

In a series of five cases treated by the author, "adreson" (cortisone), 50 mg. daily, was used in some cases and prednisone, 10 mg. daily, in others. Treatment lasted for at least 12 to 14 days, and was combined with amidopyrine, salicylates, and sedatives. In all cases hyperkinesis ceased within a fortnight, but treatment was continued if signs or symptoms of active rheumatism remained. The only recurrence occurred in a pregnant woman aged 22 with a 7-year history of chorea and mitral disease. She received cortisone, 50 mg. daily for 4 days, followed by prednisone, 20 mg. daily for 10 days, by which time all choreic movements ceased. A week later there was a slight recurrence in the left hand, which disappeared in 4 days on resumption of treatment. She received in all 350 mg. cortisone and 440 mg. prednisone. Her pregnancy terminated with a normal live birth and there were no more relapses.

L. Firman-Edwards.

Blood Groups in Acute Rheumatism. ADDIS, G. J. (1959). *Scot. med. J.*, **4**, 547. 7 refs.

The known facts concerning the aetiology of acute rheumatism suggest the existence of an inherited factor influencing the immunological behaviour of the host. A survey of patients with rheumatic heart disease indicates that the ABO blood group system does not contain this hypothetical factor.—[*Author's summary.*]

Effectiveness and Limits of Action of Synthetic Pyrazol Derivatives in Rheumatic Fever in Childhood. (Efficacia e limiti d'azione nella malattia reumatica, in campo pediatrico, dei derivati pirazolici di sintesi.) MACCIOTTA, A. (1959). *Ann. ital. Pediat.*, **12**, 425. 8 refs.

Leucocytosis as a Complication of Prednisone Therapy in Rheumatic Fever. HARRIS, T. N., and VANDEGRIFT, H. N. (1960). *Pediatrics*, **25**, 80. 3 figs, 8 refs.

Chronic Articular Rheumatism (Rheumatoid Arthritis)

Influence of Chrysotherapy followed by Chloroquine Therapy upon the Hemagglutination Reaction in Rheumatoid Arthritis. [In English.] MICHOTTE, L., and VANSLYPE, J. (1959). *Acta rheum. scand.*, **5**, 148. 14 refs.

From the University of Louvain the authors report the results of the differential sheep-cell agglutination reaction in 65 cases of rheumatoid arthritis classified as "definite" according to the American Rheumatism Association criteria. Positive reactions (1 : 32 or higher) were obtained in 49 cases. In a control series of 62 subjects who showed no evidence of joint or collagen disease, four positive results occurred. It was found that those sero-positive patients whose disease had been established more than one year tended to give a high titre, suggesting that the agglutination titre increases with time.

The 49 sero-positive patients received a weekly intravenous injection of 100 mg. aurothiopropanol sulphanate for 12 weeks; no toxic effects were observed. After this course the agglutination reaction of seventeen of these cases was found to be negative (titre 1 : 16 or less), and in a further twelve the titre showed some reduction. These changes, however, occurred very largely among those patients with a disease of less than a year's duration. The same 49 patients were then given chloroquine by mouth in doses of 100 to 300 mg. daily and were observed for 15 to 18 months. At the end of that time a further sixteen patients had become sero-negative and only in five cases was the titre still unchanged. Again, most of this improvement occurred in those cases with disease of less than one year's duration, but cases of longer standing now also showed some improvement.

The authors discuss the question whether this change in titre (which is statistically significant) was due to the treatment or whether it was merely due to spontaneous remission occurring in the natural course of the disease. They claim that the chances of obtaining a reduction in titre are greater with combined gold and chloroquine therapy than with gold alone. *B. E. W. Mace.*

Effect of Amodiaquin (Camoquin) on the Course of Rheumatoid Arthritis. POMEROY, H., WARREN, C., MILLS, D., and CLARK, G. M. (1959). *Arthr. and Rheum.*, **2**, 396. 1 fig., 5 refs.

The value of the antimalarial compound amodiaquin ("camoquin") in the treatment of chronic rheumatoid arthritis was investigated at the Shelby County Hospital, Memphis, Tennessee, on seven elderly patients, of an average age of 72 years, who had suffered from arthritis for periods ranging from 10 to 55 years. Four 50-mg. tablets of amodiaquin or similar tablets of a placebo were administered daily, the double-blind technique being employed. Each week the observers measured Lansbury's "systemic index" for rheumatoid arthritis, based on duration of morning stiffness, time of onset of fatigue, grip strength, and rapidity of the erythrocyte sedimentation rate; in addition, a note was made of the amount of aspirin consumed.

The final assessment, which was made at the end of 12 weeks, showed that amodiaquin therapy had produced a significant and prolonged effect upon the Lansbury index. Apparently the drug had produced moderate suppression of inflammation, while at the same time subjective improvement was also recorded.

With reference to the possible side-effects of the drug, the authors report that nausea and vomiting developed in three out of 32 patients attending the out-patient clinic of the hospital for amodiaquin therapy, while a patient with a history of cholelithiasis began to show signs of jaundice during the 16th week of therapy and eventually died in hepatic coma. Another patient recovered completely after an illness which resembled afebrile infective hepatitis. *A. Garland.*

15-Month Controlled Study of the Effects of Amodiaquin (Camoquin) in Rheumatoid Arthritis. BEPLER, C. R., BAIER, H. N., MCCRACKEN, S., RENTSCHLER, C. L., ROGERS, F. B., and LANSBURY, J. (1959). *Arthr. and Rheum.*, **2**, 403. 3 figs, 10 refs.

A trial, by the double-blind technique, of amodiaquin and a placebo in the treatment of fourteen patients with chronic rheumatoid arthritis is reported from Temple University School of Medicine, Philadelphia. Since an initial dosage of amodiaquin of 400 mg. daily gave rise to toxic symptoms, this dose was reduced to 200 mg., but a few patients were unable to tolerate even a dosage as low as 70 mg. daily. Clinical assessment after 5 to 10 months revealed that the treatment had reduced the activity of the disease by about 50 per cent. and that patients who had formerly required an average daily dose of 7·5 mg. prednisone now needed only 2 mg. Statistical evaluation of the combined "Systemic and Articular Indexes" supplied additional evidence that a major improvement had taken place. Unfortunately a slow relapse occurred in all cases after the discontinuance of treatment.

The pronounced toxic symptoms mentioned above produced by amelioration in a dosage of 400 mg. daily, administered as a powder in capsules, included diarrhoea, vomiting, abdominal cramp, tremor, and mental depression, these manifestations subsiding soon after treatment was discontinued. However, tablets of the drug produced relatively mild disturbances. Some patients complained of nausea, others lost weight, but leucopenia was not observed. One patient died of malignant hepatoma, which, however, could not be attributed to the treatment. As three fatal cases following amodiaquin

therapy have been reported in the literature, it is recommended that the drug should not be employed in the routine treatment of rheumatoid arthritis. In many respects the toxic effects of the drug resemble those of chloroquine, but there is evidence that a special association exists between amodiaquin therapy and hepatic damage, sensitization, and severe exacerbations after discontinuance of the drug. *A. Garland.*

Roentgen Manifestations of Senile Rheumatoid Arthritis. [In English.] SOILA, P., and OKA, M. (1959). *Acta rheum. scand.*, **5**, 206. 11 figs, 11 refs.

At Kivelä Hospital, Helsinki, an analysis was made of the radiological appearances of the hands, feet, ankles, and knees of 115 patients (22 male and 93 female) aged 50 years and over in whom the duration of rheumatoid arthritis was 6 years or less. Severe changes, including deformities and ankyloses, were observed even within the first 18 months of the onset of the disease. Soft tissue changes were easily discernible. Cystic changes were of little diagnostic value, since they are common in a number of conditions especially in this age group, but superficial eruptions of the cortex and expansions of cysts to the surface of the bone were reliable radiological manifestations of rheumatoid arthritis in this as in other age groups. Periosteal elevation and thickening were not seen. The authors state that rheumatoid arthritis in old age is not a quiescent process. They claim that in spite of the known unfavourable effects of age itself joint-space changes, deformities, carpal fusions, and ankyloses are less common in "senile" arthritis than in rheumatoid arthritis in younger patients. [The validity of this would be easier to assess if the age distribution of the group and the method of case selection were given: "senile" is scarcely a valid description for the whole group.] *J. N. Agate.*

Rheumatoidlike Arthritis in Swine. SIKES, DENNIS.
Swine Erysipelas and Arthritis. SHUMAN, RICHARD D.
Does Vaccination against Swine Erysipelas afford Protection against Arthritis? NEHER, GEORGE M., and SWENSON, CHARLES B.
(1959). *Lab. Invest.*, **8**, 1406, 1416, 1419.

Swine erysipelas results from infection with *Erysipelothrix rhusiopathiae*, but the morbidity and clinical and pathological manifestations, as well as the mortality, are extremely variable. In the acute septicaemic form the animal is febrile and reddish purplish areas may develop on the skin, usually with leucopenia and monocytosis. If the fever remains high for 36 to 48 hours, the animal frequently dies. The pathological changes are not specific, but the most characteristic one is that seen in the skin with distension of blood vessels, hyperaemia, enlarged papillae, and small haemorrhages. This vascular involvement with haemorrhages may occur in any tissue, particularly the heart, liver, lymph nodes, kidneys, and gastro-intestinal tract. If the animal survives this phase, acute arthritis may develop 2 to 3 weeks later. Pathologically there is vascular engorgement of the joint capsule and synovial tissues, with varying degrees of oedema followed by proliferation of synovial villi. The acute swelling frequently subsides in 2 to 3 weeks, although it sometimes persists, and if it continues for 2 months or more, severe joint changes occur and recovery is unlikely. Pathologically there is marked proliferation of synovial villi with pannus formation, erosions, and destruction of cartilage.

The incidence of micro-organisms found in joints has varied considerably, Sikes and his workers having been unable to isolate the organisms in animals showing advanced chronic arthritis 32 weeks after exposure to infection, while Hughes found them up to 83 weeks after experimentally-induced arthritis, and Shuman found them in seven of nine joints examined 57 weeks after percutaneous exposure. It has been suggested that, in this chronic arthritis, the lesion may resolve and the joint recover, or fibrosis may allow healing but with intra-articular adhesions, or the synovial granulation tissue may continue to extend assuming the properties of a benign neoplasm. This last explanation would account for the persistence of arthritis in the absence of micro-organisms. The economic aspect of this arthritis in swine is serious as it is one of the commonest causes of carcases being condemned, and much work has been done on immunization against it. However, it is still not certain whether vaccination protects against arthritis. The experiments described by Neher and Swenson were designed to assess the effect when vaccinated pigs were challenged by intravenous or percutaneous cultures of *E. rhusiopathiae*. Vaccination undoubtedly protected the animals from the acute illness, arthritis developed in all those challenged intravenously at 3 months, and in two of the three challenged at 4 months; no arthritis developed in those challenged by scarification at 3 months, but it was seen in two of the four challenged this way at 4 months. From this experimental work it is suggested that sensitivity is a factor in the development of this disease and may explain the pathology in affected joints which are apparently sterile. *B. M. Ansell.*

Place of ACTH in the Treatment of Rheumatoid Arthritis. (La place de l'ACTH dans le traitement de la polyarthrite rhumatoïde.) COSTE, F., CAYLA, J., and JONCHÈRES, Y. (1960). *Sem. Hôp. Paris*, **36**, 411. 69 refs.

Rheumatoid Arthritis in Childhood. Involvement of the Hip. SHANDS, A. R., and MUEHE, C. C. (1960). *Delaware St. med. J.*, **32**, 1. 15 figs, 6 refs.

Corticotrophin and Corticosteroid Therapy in Rheumatoid Arthritis. (Corticotropin og corticosteroidterapi ved kronisk polyartritt.) SOLEM, J. H., and RØMCKE, O. (1960). *Nord. med.*, **63**, 11. 2 figs, 9 refs.

Rheumatoid Micro-angiitis. (La microangioite reumatoide.) LUCHERINI, T., CECCHI, E., and MASDEA, E. (1960). *Minerva med.* (*Torino*), **31**, 171. 39 figs, 92 refs.

Contribution to the Treatment of Rheumatoid Arthritis by Irradiation of the Adrenals combined with Microperfusions of Whole Blood. (Contribution au traitement de la polyarthrite chronique évolutive par radiothérapie des surrénales associée à des microperfusions de sang total.) STOIA, I., GHENTU, E., ZIGURA, V., PANDELESCU, L., DUMITRESCU, G., and (1959). *Rhumatologie*, **11**, 292.

Rheumatoid Arthritis with Chronic Pulmonary Changes. (Primär chronische Polyarthritis mit chronischen pulmonalen Veränderungen.) BRAUNSTEINER, H., EGGHART, F., and POTUZHEK, O. (1960). *Dtsch. med. Wschr.*, **85**, 115. 21 refs.

Observations and Results of Prolonged Treatment with Chloroquine in Rheumatoid Arthritis. (Osservazioni e risultati del trattamento protratto con clorochina nell'artrite reumatoide.) PORTELLA, A., and COLAO, G. (1960). *Rif. med.*, **74**, 69. 34 refs.

Research on the Treatment of Rheumatoid Arthritis with Combinations of Steroids. 2. Triamcinolone + Dexamethasone. (Richerche sulla cura dell'artrite reumatoide con associazioni steroidee. Nota 2. Associazione triamcinolone con desametasone.) ROBECCHI, A., and DI VITTORIO, S. (1959). *Reumatismo*, **11**, 307.

Intracranial Manifestations in Two Cases of Systemic Rheumatoid Disease. STEINER, J. W., and GELBLOOM, A. J. (1959). *Arthr. and Rheum.*, **2**, 537. 9 figs, 19 refs.

(Osteo-Arthritis)

Degenerative Arthritis in the Bovine. SHUPE, JAMES L.

Pathogenesis of Osteo-Arthritis in the Horse. TRUM, BERNARD F.

Osteo-Arthritis in Laboratory Animals. SOKOLOFF, LEON.

Observations in the Clinical Signs and Gross Pathology of Degenerative Joint Disease in Aged Bulls. NEHER, GEORGE M., and TIETZ, WILLIAM J., JR.

Kinetics of Osteo-Arthritis. JOHNSON, LENT C. (1959). *Lab. Invest.*, **8**, 1190, 1197, 1209, 1218, 1223.

The aetiology of degenerative arthritis in the bovine is unknown. The condition consists in degeneration of joint cartilage and secondary involvement of the bone, unaccompanied by systemic manifestations; it occurs in older animals in the larger freely mobile joints and is characterized by pain on standing and moving. With the horse both sexes and any age may be affected, and the arthritis is thought to arise as a result of dietary imbalance in the calcium and phosphorus ratio. Although the serum calcium and phosphorus levels remain normal, the total bone content of calcium and phosphorus is reduced, while nitrogen, osseous protein, magnesium, and sulphate are all increased. Clinically it is characterized by obscure lameness followed by joint soreness, arthritis, and finally gross thickening of the bones. As yet, the progressive pathology is inadequately described. In the osteo-arthritis of laboratory animals, that of mice closely simulates its mammalian counterpart in its fundamental anatomical characteristics; local factors influence its development and affect animals as they grow older. Genetic factors are also important, but the level at which these operate is not yet certain. Observations on bulls show a high incidence with advancing age and some species are particularly susceptible. The clinical features are stiffness and lameness causing a characteristic gait. Pathologically, the disease tends to be polyarthritic with degeneration and erosion of articular cartilage and hypertrophy of bone with lipping and spur formation in the absence of synovitis.

In considering the kinetics of degenerative joint disease, Johnson comments on the fact that articular cartilage is an active living tissue, which grows particularly in youth but continues at a slower rate for many years. Once growth has ceased the continuous remodelling of bone by osteoclastic absorption and osteoblastic repair, may give rise to subchondral cysts. These result from oedema of the subchondral marrow followed by proliferation and the development of mucinous fibrillary fatty marrow with telangiectasia of the sinusoid, which expands as a result of its increasing fluid content. Expansion is associated with osteoclastic resorption of neighbouring bone trabeculae, followed by osteoblastic activity in the building of a bony wall about the cyst. Marginal lipping is also part of bone remodelling and may arise from upwards and lateral cartilage growth, local periosteal new bone formation, and chondrification of a tendon or capsule. In addition, throughout life, the cartilage constantly sheds surface fragments and this is balanced by slow replacement from the midzone. Alterations in this turn-over can be induced by exercise and by disease such as acromegaly, as well as by posture and occupational stresses of joints. As articular cartilage ages it tends to become pigmented and lose its translucency, and it develops grooves, pits, and ulceration. These changes are not uniform throughout the body, and the characteristic order of the changes precludes not only ageing but also weight-bearing as simple factors in the development of osteo-arthritis. Localization of certain joints, *e.g.* the thumb in labouring males, suggests that tangential shearing is essential in the localization of age changes in man.

Osteo-arthritis occurs at local sites of excessive cartilage abuse, and in its milder forms it cannot be separated from normal age changes. Symptoms do not seem to arise until eburnation of the underlying bone and gross irregularity of the joint surface has developed. It is suggested that primary osteo-arthritis is due to local dysplastic joint remodelling where the degree of remodelling demanded by mechanical stresses exceeds the capacity of the cartilage to respond in an orderly manner. This process is frequently associated with certain constitutional types. Secondary osteo-arthritis results from alterations in any of the factors involved in cartilage remodelling, growth, and turn-over, such as postural abnormalities requiring much remodelling, urate or homogentisic acid deposits, longstanding pannus, direct

trauma, or aseptic necrosis. The exact mechanisms are unknown and the interpretation of the known facts requires further study. *B. M. Ansell.*

Aetio-pathogenic Components of Posterior Lumbar Osteo-Arthritis. (Les composantes étio-pathogéniques de l'arthrose lombaire postérieure.) DE SÈZE, S., and WELLINGER, C. (1960). *Sem. Hôp. Paris*, **36**, 492. 7 figs.

Surgery of the Hip-Joint. Present and Future Developments. CHARNLEY, J. (1960). *Brit. med. J.*, **1**, 821. 7 figs, 1 ref.

Operative Treatment of Osteo-Arthritis of the Hip. RING, P. A. (1960). *Brit. med. J.*, **1**, 827. 3 figs, 13 refs.

Ageing and Osteo-Arthritis. TRUETA, J., and LIMA, C. (1959). *Gerontologia clin. (Basel)*, **1**, 283. 11 refs.

(Spondylitis)

Ankylosing Spondylitis—A Special Form of Rheumatoid Arthritis. (Morbus Bechterew, sonderform der primär chronischen polyarthritis?) FELLMANN, N., and WAGENHÄUSER, F. (1960). *Schweiz. med. Wschr.*, **90**, 153. 1 fig., 27 refs.

Localized Destructive Lesions in Rheumatoid Spondylitis. WHOLEY, M. H., PUGH, D. G., and BICKEL, W. H. (1960). *Radiology*, **74**, 54. 3 figs, 6 refs.

Preliminary Results of Paper-Electrophoretic Studies of Ankylosing Spondylitis. (Vorläufige Ergebnisse papierelektrophoretischer untersuchungen bei Morbus Bechterew.) PETERSEN, D. (1960). *Z. Rheumaforsch.*, **19**, 25. 9 figs, 13 refs.

Radiology of Ankylosing Spondylitis. GRAINGER, R. G. (1960). *Rheumatism*, **16**, 3. 1 fig., 14 refs.

Research and Considerations on Vertebral Ankylosing Rheumatism and the Nosography Thereof. ROBECCHI, A., and DANEO, V. (1959). *Arch. interamer. Rheum.*, **2**, 410. 7 figs, 45 refs.

(Miscellaneous)

Appraisal of Phenylbutazone Suppositories. HAWKINS, C. F., and FAWNS, H. T. (1959). *Brit. med. J.*, **2**, 740. 2 figs, 24 refs.

Phenylbutazone in suppository form was given to nineteen patients with rheumatoid arthritis, two with ankylosing spondylitis, and five with osteo-arthritis. All except two of the patients suffered from dyspepsia, which was due to peptic ulcer in fourteen, to hiatus hernia in two, and to oral phenylbutazone therapy in five; in three the cause was not known.

A suppository containing 250 mg. phenylbutazone was inserted into the rectum each night; in some cases two were given in the 24 hours. In order to assess the absorption of the drug from the rectal mucosa the serum phenylbutazone level was determined, a modification of Pulver's method (*Schweiz. med. Wschr.*, 1950, **80**, 308) being used. With a dosage of one suppository daily, the serum phenylbutazone level was above 8 mg. per 100 ml. in twelve of the 26 patients and above 4·6 mg. per 100 ml. in ten, most of whom had satisfactory relief of pain. With a dosage of two suppositories daily, the serum phenylbutazone level increased to a more effective therapeutic range. In four patients the blood level was low—between 1 and 5 mg. per 100 ml.—with a dosage of one suppository daily, but in two of these a satisfactory level was achieved when the dose was increased to two suppositories daily. The suppositories were given for less than 6 months to eight patients, one year or longer to six, and 6 months or longer to twelve. Phenylbutazone dyspepsia disappeared when suppositories were substituted for tablets and none of the peptic ulcer patients experienced an exacerbation of symptoms.

C. E. Quin.

Non-specific Arthritis in Children: a Review of 105 Cases, 1931 to 1958. KUDELKA, P. (1959). *Med. J. Aust.*, **2**, 508. 5 refs.

In an attempt to determine whether non-specific arthritis is a disease entity or merely a classification for mild or atypical forms of recognized joint diseases, 105 consecutive cases admitted to the Royal Children's Hospital, Mount Eliza, Victoria, Australia, between 1931 and 1958 were reviewed and the present state of health of all the patients who could be traced (58) was assessed. The diagnosis was based essentially on the elimination of recognized causes of arthritis, but the author considers that there was a characteristic pattern in the series which justified their preliminary classification under one heading. Of the 105 patients, 46 were males and 64 females, and their ages ranged from 2 to 14 years. The weight-bearing joints were chiefly affected, and in most cases the condition was monarticular. The onset was usually insidious, the symptoms commonly being loss of function, swelling, and pain or discomfort in the joint. General health was usually good and loss of weight was not a feature. A number of investigations were carried out, but only the erythrocyte sedimentation rate (E.S.R.) and the radiological appearances were found to be of any real value. The author states that no specific treatment is known and the general principles adopted were prolonged immobilization until the E.S.R. and *x*-ray findings suggested quiescence. Most of the patients remained in hospital for 3 to 6 months, but 20 per cent. remained for a year or more. Of the 58 followed up, one died from a cerebral tumour 12 years after discharge; the remaining 57 were well, and there was no tendency for symptoms to recur even after many years.

It is concluded that non-specific arthritis is a sub-acute predominantly monarticular panarthritis of obscure

aetiology, but may have an association with infection. In general the condition carries a good prognosis.

J. M. Smellie.

Choline Salicylate: An Effective, Well-tolerated Drug for Treatment of Rheumatic Diseases. SCULLY, F. J. (1960). *Sth. med. J.* (*Bgham, Ala.*), **53**, 12. 13 refs.

Trial of a New Muscle Relaxant in Rheumatological Practice. (Essai d'un nouveau décontractant en pratique rhumatologique.) THEVENOZ, F. (1959). *Rhumatologie*, **11**, 287.

Relationship of Hysterectomy to Chronic Arthritis. KERR-TAYLOR, H. (1960). *Rheumatism*, **16**, 17. 17 refs.

Gout

Preliminary Report on G 28315 in the Treatment of Gout. RODEN, D. (1960). *J. Irish med. Ass.*, **46**, 22. 4 refs.

Observations on the Uricosuric Activity of Zoxazolamine. (Osservazioni sull'attivita uricosurica della zoxazolamina.) RATTI, G., and CIRLA, E. (1959). *Reumatismo*, **11**, 342. 2 figs, 6 refs.

Pararheumatic (Collagen) Diseases

New Clinical Concept of Systemic Lupus Erythematosus. RUPE, C. E., and NICKEL, S. N. (1959). *J. Amer. med. Ass.*, **171**, 1055. 2 figs, 11 refs.

The natural history of systemic lupus erythematosus was studied at the Henry Ford Hospital, Detroit, in the medical records of 100 cases, in 83 of which a positive response had been obtained to the L.E.-cell test. From the analysis of the findings the authors consider that the disease runs a benign course (more than half of the patients survived at least 10 years) and is more common in males (34 in the series) than was previously thought to be the case. It is a less serious disease in males than in females. The occurrence of a streptococcal infection immediately before the onset is considered to be of aetiological significance. The prognosis was poor in patients with a butterfly rash or neurological manifestations, but appeared to be good in patients with a rheumatoid-like arthritis. *M. Wilkinson.*

Psychoses associated with Systemic Lupus Erythematosus. O'CONNOR, J. F. (1959). *Ann. intern. Med.*, **51**, 526. 2 figs, 21 refs.

The psychiatric manifestations of systemic lupus erythematosus were studied in forty patients admitted to the Columbia Presbyterian Medical Center, New York. During a follow-up period which averaged 3 years, psychoneurotic symptoms developed in five patients and one or more psychotic episodes occurred in 21 patients. The psychotic episodes were diagnosed as schizophrenic reactions in nine cases, as depressive reactions in three cases, and as due to acute brain symptoms, with delirium or coma, in eleven cases. Only one of the 21 psychotic patients gave a history of previous psychiatric disorder and only three were not receiving steroids at the time of the episode, which often followed an increase in dosage. The author suggests that greater disease activity rather than higher steroid dosage was correlated with the occurrence of psychotic episodes. Following remission of the disease and a reduction in the dosage of steroids, the psychiatric manifestations invariably subsided, generally within one week. Subsequent restoration of the full dosage of the steroid did not usually cause exacerbation of the psychosis, and the author therefore recommends that steroid therapy need not be withdrawn because of psychiatric symptoms if its use is indicated for other aspects of the disease.

Of eleven cases which came to necropsy, ten showed evidence of brain damage secondary to endarteritis, and in all of these psychiatric or neurological syndromes had been present during life. *M. Wilkinson.*

False-positive Results with the *p*-Toluene-sulfonic Acid Precipitation Test for Systemic Lupus Erythematosus. [In English.] JULKUNEN, H., KAIPAINEN, W. J., and PALVA, I. (1959). *Acta rheum. scand.*, **5**, 223. 3 refs.

Some workers have found that the simple precipitation test for the diagnosis of systemic lupus erythematosus (S.L.E.) described by Jones and Thompson (*J. Amer. med. Ass.*, 1958, **166**, 1424; *Abstr. Wld Med.*, 1958, **24**, 214) is unreliable for both this purpose and for the differentiation of S.L.E. from rheumatoid arthritis. The present authors have carried out this test, in which the reagent is a 12 per cent. solution of *p*-toluene-sulphonic acid in glacial acetic acid, in 259 patients at the Rheumatism Foundation Hospital, Heinola, Finland. In all the patients the erythrocyte sedimentation rate (E.S.R.) was raised. The results of the test were positive in all four patients with S.L.E., and in eight of fifteen with rheumatoid arthritis and a positive L.E.-cell reaction. In fifteen out of 124 patients with typical rheumatoid arthritis, the test gave false-positive results, and in all seven cases of ankylosing spondylitis the response was negative. False-positive results were also obtained in twenty out of 100 moderately ill patients suffering from various diseases. However, the results were negative in 65 out of 66 healthy subjects.

It is concluded that the findings in this investigation (18 per cent. false-positive results in 259 cases) do not support the early view that the test is of value in the differential diagnosis of S.L.E. *D. Preiskel.*

Ophthalmoscopic Signs in Collagen Diseases (Temporal Arteritis, Disseminated Lupus Erythematosus, Serum Disease, Dermatomyositis, Scleroderma). [In Rumanian.] LASCU, F., NICULESCU, M., and NICULIU, I. (1959). *Oftalmologia* (*Bucureşti*), **3**, 239. 1 fig., 14 refs.

Ophthalmoscopic manifestations in collagen disease are particularly important in diagnosis. In periarteritis nodosa and in temporal arteritis, they are almost symptomatic but they are rare in lupus, dermatomyositis,

and scleroderma; they may be seen in Gougerot-Sjögren's syndrome.

Vascular lesions of the optic nerve can cause pseudo-papillitis, retrobulbar pseudo-neuritis, optic atrophy, and pseudo-glaucoma; vascular lesions in the retina are indicated by collagen retinopathy, and those in the choroid by choroidal nodules.

Unlike strictly local signs, hypertensive retinopathy and the consequent retinal detachment and papilloedema are repercussions of arterial hypertension or hypertensive encephalopathy, the usual complications of these affections which can occur in a more advanced stage of the evolution of certain collagen disease.

The visual prognosis is serious and can also aggravate the general prognosis.—(*Authors' summary.*]

Contribution to the Clinical and Histological Study of Chronic Disseminated Lupus Erythematosus of the Nails. (Contributo alla conoscenza clinica ed istologica del lupus eritematoso cronico disseminato del complesso ungueale.) SANNICANDRO, F. (1960). *Minerva derm.* (*Torino*), **35**, 32. 4 figs, 5 refs.

Dermatomyositis, Disseminated Calcinosis, and Metaplastic Ossification—Clinical Studies over a Period of 7 years in a Female with Rheumatoid Arthritis. TALBOTT, J. H., KOEPF, G. F., CULVER, G. J., and TERPLAN, K. (1959). *Arthr. and Rheum.*, **2**, 499. 11 figs, 9 refs.

General Pathology

Elimination of Heterophil Agglutinins and Inhibitors in Serum simultaneously with the Precipitation of the Rheumatoid Factor. Preliminary Report. [In English.] SVARTZ, N., and SCHLOSSMANN, K. (1959). *Acta med. scand.*, **164**, 529. 6 refs.

The authors have previously shown that the haem-agglutination test for rheumatoid arthritis can be improved by the separation of a moeity from whole serum by cold precipitation methods. This improvement consists mainly in increased specificity by the elimination of positive agglutination reactions due to pathological processes other than that of rheumatoid arthritis, and particularly systemic lupus erythematosus. In this paper from the King Gustav V Research Institute, Stockholm, further improvements are reported, both in regard to results and in regard to the practicability of the procedure for routine use in clinical laboratories.

The new procedure consists in a modified method of fractionation of the serum with ammonium sulphate. To 1 ml. inactivated serum is added 2 ml. physiological saline and then, drop by drop, 1·3 ml. saturated ammonium sulphate. This results in a final concentration of ammonium sulphate of 1·23 M. It is shown that the precipitate thus obtained contains almost all the rheumatoid factor. Furthermore, it is found that by this technique the substances having an inhibitory activity remain in the supernatant fluid, as also do the heterophil agglutinins. The technique thus obviates the necessity for absorption of the heterophil agglutinins in the standard sheep-cell test and eliminates the inhibitory substances of the reaction together with the agglutinins associated with other diseases. The question whether this technique further increases the specificity of this test as a diagnostic method for rheumatoid arthritis is to be considered in a later report. *Harry Coke.*

Concentration of Hyaluronic Acid in Synovial Fluid. DECKER, B., MCGUCKIN, W. F., MCKENZIE, B. F., and SLOCUMB, C. H. (1959). *Clin. Chem.*, **5**, 465. 11 refs.

In this study reported from the Mayo Clinic, the concentration of hyaluronic acid in synovial fluid was measured by Dische's carbazole reaction in a protein-free filtrate after digestion with hyaluronidase. Non-hyaluronic acid sources of colour were determined and their effect rendered minimal by dilution of the protein-free filtrate; this source provides a maximum error of 10 mg. per 100 ml. The mean concentration of hyaluronic acid in synovial fluid of patients without rheumatic disease was 321 mg. per 100 ml. In fluid from patients with traumatic arthritis, osteo-arthritis, and probable rheumatoid arthritis, the value ranged from 170 to 188 mg. per 100 ml., while in fluid from patients with definite rheumatoid arthritis the mean concentration was 115 mg. per 100 ml. Synovial fluid from peripheral joints involved in "rheumatoid spondylitis" showed an even lower mean of 102 mg. per 100 ml. No change in the concentration was found in four patients one week after the intra-articular injection of hydrocortisone. In the patients with rheumatoid arthritis no correlation was apparent between the fluid level of hyaluronic acid and the duration of the disease. It is suggested that there is an inverse relationship between the concentration of hyaluronic acid in the synovial fluid and the degree of systemic inflammation as measured by the protein-bound hexose level in the serum. *Harry Coke.*

Significance of Hematoxylin Bodies in the Necropsy Diagnosis of Systemic Lupus Erythematosus. WORTHINGTON, J. W., JR., BAGGENSTOSS, A. H., and HARGRAVES, M. M. (1959). *Amer. J. Path.*, **35**, 955. 5 figs, 22 refs.

Hematoxylin bodies were found in seventeen of twenty consecutive necropsy cases of systemic lupus erythematosus [at the Mayo Clinic]. They were seen most frequently in the presence of classic clinical and pathological features, but were also encountered in multiple organs even in less typical cases. The single hematoxylin body could not always be distinguished from nuclei undergoing karyolysis or from other infrequently encountered substances with similar appearance. These substances, when observed in other conditions, were located in areas of necrosis or appeared as isolated findings. Criteria for the identification of hematoxylin bodies were designed to distinguish them from simulative material and were used in this investigation. When a number of bodies meeting these criteria were identified in a given case, their specificity appeared to be of high degree and to be greater than that of any other anatomic feature of

the disease. This specificity, coupled with their occurrence in the majority of cases of disseminated lupus erythematosus, indicates that hematoxylin bodies constitute highly significant and useful diagnostic features. —[*Authors' summary.*]

Serology of the Rheumatic Agglutination Factor. (Zur Serologie des Rheumaagglutinationsfaktors.) WIEDERMANN, G., and REINHARDT, F. (1959). *Wien. Z. inn. Med.*, **40**, 303. 11 refs.

An investigation was carried out at the Second Medical Clinic of the University of Vienna to determine whether the rheumatoid agglutination factor develops from globulins present in normal serum or whether it is based on a protein component not normally present. On the assumption that, if the factor develops from normal serum globulins, it should react with anti-human globulins such as Coombs serum, a latex-*y*-globulin system was saturated with rheumatoid factor and then incubated with Coombs serum. No significant fall in the titre of the Coombs serum, which would have indicated that a reaction with the rheumatoid factor had occurred, was found after incubation. It is therefore concluded that the rheumatoid agglutination factor is not a component of normal human serum. *G. W. Csonka.*

Serum Glycoproteins in Rheumatic Fever and in the Active Phase of Rheumatoid Arthritis. (Le glicoproteine del siero nel ruematismo articolare acuto e nel l'artrite ruematoide in fase attiva.) BUSCARINI, L., and BARONCELLI, G. (1959). *Progr. med.* (*Napoli*), **15**, 528. 2 figs, 48 refs.

The value of determination of the serum glycoprotein level as a measure of rheumatic activity has been clearly demonstrated. In addition, various workers have attempted to define the fundamental modifications of the serum glycoproteins in the course of acute rheumatism and rheumatoid arthritis as an index of the evolutive stage of the disease. In acute rheumatism it has been found that an increase occurs in the glycoprotein level which is mainly due to an increase in carbohydrate bound to the α_2-globulin fraction and is closely correlated with the activity of the disease process. In the active phase of rheumatoid arthritis changes in the serum glycoproteins are analogous to those found in rheumatic fever, but are quantitatively less marked. During the latent phase of rheumatoid arthritis the levels of protein-bound carbohydrates are normal. During the decline of activity of both diseases the serum glycoprotein levels diminish in the same degree, but may rise again when treatment is suspended.

These findings have been confirmed by the present authors, working at the Institute of Clinical Medicine and Therapeutics of the University of Pavia, in investigations on 22 patients aged 16 to 40 years, of whom fourteen were suffering from acute articular rheumatism and eight from rheumatoid arthritis in the active phase. A total of 33 blood specimens obtained from these patients by venepuncture at various stages were examined and compared with the findings in specimens from thirty healthy individuals aged 18 to 42 years. Diagnosis in the rheumatic cases was established on clinical grounds and confirmed by estimation of the erythrocyte sedimentation rate, antistreptolysin titre, and C-reactive protein level. It is concluded that estimation of the serum glycoprotein level, and in particular of the ratio of α_2-globulin-bound carbohydrate to total α_2 globulin, constitutes the best method of estimating the degree of remission or persistence of the morbid process in rheumatic diseases. *Robert E. Lister.*

The Paradox of the Antibody Response to Streptodornase: the Usefulness of Antidesoxyribonuclease B as an Indication of Streptococcal Infection in Patients with Acute Rheumatic Fever. WANNAMAKER, L. W. (1959). *Amer. J. Med.*, **27**, 567. 8 figs, 10 refs.

Tests for neutralizing antibody to deoxyribonucleases have been considered a poor index of preceding streptococcal infection in patients with rheumatic fever. The author of this report from the Rockefeller Institute, New York, has previously observed that three serologically distinct deoxyribonucleases (A, B, and C) are produced by Group-A streptococci. He now shows that antibody to deoxyribonuclease B occurs regularly following streptococcal infection, but rarely to A and C. Previous antibody studies for streptococcal deoxyribonuclease employed a strain of Group-A streptococci which produced primarily deoxyribonuclease A.

The serum antibody titres to streptococcal deoxyribonucleases A, B, and C were compared in 41 patients with acute rheumatic fever, 50 control subjects, and 57 patients with untreated Group-A streptococcal infection. The test depends on the inhibition of enzyme activity (from streptococci known to produce deoxyribonuclease A, B or C) by dilutions of active sera, as shown by the formation of a fibrous precipitate produced by the action of alcohol on a solution of deoxyribonucleate. In addition comparisons were made between the frequency and magnitude of the antideoxyribonuclease response and the anti-streptolysin-O titres. The author considers that the antideoxyribonuclease -B test appears to be slightly more sensitive than the antistreptolysin-O test and that the former is particularly useful in patients with rheumatic fever who present with low or borderline antistreptolysin-O titres. *D. M. Weir.*

Protein-bound Carbohydrate in the Serum and Intercellular Fluid in Rheumatoid Arthritis and Arteriosclerosis Obliterans. (Über proteingebundene Kohlenhydrate des Serums und der Intercellularflüssikeit bei chronischer Polyarthritis rheumatica und bei Arteriosclerosis obliterans.) EMMRICH, R., and BANNERT, N. (1960). *Ärztl. Wschr.*, **15**, 115. 21 refs.

Latex Test in Rheumatology (Critical Study of Preliminary Results). (Le test au "Latex" en rhumatologie. Étude critique de nos premiers résultats.) VINCENT, G., JR., HENNINOT, E., and DUHAMEL, M. (1959). *Rhumatologie*, **11**, 282. 21 refs.

Immunological Problems in Rheumatoid Arthritis. (Problèmes immunologiques de la polyarthrite chronique évolutive.) EYQUEM, A., JACQUELINE, F., PODLIACHOUK, L., and FRANCQ, J.-C. (1960). *Rev. franç. Ét. clin. biol.*, **5**, 58. 17 refs.

Differentiation of Various Antibodies against Nuclear and Cytoplasmic Cell Constituents in Disseminated Lupus Erythematosus. (Zur Differenzierung verschiedener Antikörper gegen nucleäre und cytoplasmatische Zellbestandteile bei Lupus erythematosus disseminatus.) DEICHER, H. (1960). *Klin. Wschr.*, **38**, 104. 3 figs, 14 refs.

Localization of the Rheumatoid Factor in the Serum Proteins and its Amino-acid Content. (Localizzazione del fattore reumatoide nelle sieroproteine e sua composizione in aminoacidi.) ANTONACI, B. L., RAVAIOLI, P., BRACONI, M., DEL GIOVANE, L., and RAVENNI, G. (1959). *Reumatismo*, **11**, 346. 4 figs, 71 refs.

Immuno-electrophoretic Study of the Rheumatoid Factor. (Étude immuno-électrophorétique du facteur rhumatoïde.) FRANCQ, J. C., EYQUEM, A., PODLIACHOUK, L., and JACQUELINE, F. (1960). *Ann. Inst. Pasteur*, **98**, 96. 24 refs.

Antigenicity of Serological Factors in Rheumatoid Arthritis. (Antigénicité des facteurs sérologiques de la polyarthrite chronique évolutive.) PODLIACHOUK, L., FRANCQ, J. C., EYQUEM, A., and JACQUELINE, F. (1960). *Ann. Inst. Pasteur*, **98**, 90. 15 refs.

Histologic Studies on Human Synovial Membrane. I. Metatachromatic Staining and the Effects of Streptococcal Hyaluronidase. HAMERMAN, D., and RUSKIN, J. (1959). *Arthr. and Rheum.*, **2**, 546. 2 figs, 19 refs. **II. Localization of Some Oxidative Enzymes in Synovial Membrane Cells.** HAMERMAN, D., and RUSKIN, J. (1959). *Arthr. and Rheum.*, **2**, 553. 5 figs, 9 refs.

Research on the Behaviour of Antistreptolysin-O in the Serum in Rheumatoid Arthritis. (Richerche sul comportamento delle antistreptolisine-O del siero nell' artrite reumatoide.) EINAUDI, G., and GARELLI, R. (1959). *Reumatismo*, **11**, 325. 16 refs.

Comparative Evaluation of the Latex-Fixation Test and the Haemagglutination Test in the Serological Study of 659 Cases of Varied Aetiology. (Valutazione comparativa della reazione al lattice e del test di emoagglutinazione nella studio sierologico di 659 casi di malattie a varia eziologia.) AMIRA, A., and VISCONTI, A. (1959). *Reumatismo*, **11**, 315. 1 fig., 27 refs.

Histology of Synovial Tissue in Old Age. (Aspetto istologico del tessuto sinoviale nell'etá senile.) GARELLI, R. (1959). *Reumatismo*, **11**, 334. 8 figs, 15 refs.

ACTH, Cortisone, and Other Steroids

Results of Treatment with Hexadecadrol in Rheumatology. (Résultats thérapeutiques de l'hexadécadrol en rhumatologie.) RUBENS-DUVAL, A., VILLIAUMEY, J., and LUBETZKI, D. (1959). *Sem. Hôp. Paris*, **35**, 2441. 7 refs.

The widespread use of adrenocortical steroids in the treatment of rheumatoid arthritis had led to much research into the production of derivatives of these substances which would retain their anti-inflammatory and anti-allergic properties while producing fewer or less serious side-effects. In this study the authors observed the effects of one of these derivatives, dexamethasone, in the treatment of nine cases of rheumatoid arthritis, one of ankylosing spondylitis, three of lumbo-sciatica, and one of periarthritis of the shoulder. The patients were fully examined at the beginning and again after 4 to 6 weeks of treatment. The serum protein pattern was also determined electrophoretically and the erythrocyte sedimentation rate noted.

The patient with ankylosing spondylitis received between 2·5 and 3·5 mg. daily for 9 weeks; although great relief was experienced, the side-effects, such as raised blood pressure, oedema, and capillary fragility, were severe. Of the nine cases of rheumatoid arthritis, eight responded dramatically, but the ninth patient, a man aged 61 whose dosage reached 12 mg. daily, died suddenly; at necropsy the lungs showed grey hepatization and gastric ulceration was present. The activity of dexamethasone appears to be five to six times that of prednisone, enabling relatively larger doses to be given, but the authors did not find that it was well tolerated, as has been suggested in the transatlantic literature. Insomnia, for example, was very troublesome in some of their cases. The remaining four patients obtained relief from pain, such as would be expected from doses of 25 mg. delta-cortisone (prednisone). Higher doses were tolerated because of the short duration of treatment. They conclude that while the therapeutic effect of dexamethasone is considerable, its administration entails a calculated risk. *D. Prieskel.*

Remarks on 12 Months' Experience with Dexamethasone. (Remarques sur 12 mois d'éxpèrience avec la dexaméthasone.) ROBECCHI, A., and DI VITTORIO, S. (1959). *Rev. Rhum.*, **26**, 635. 26 refs.

Disturbance of Cortisol-Noradrenaline Homeostasis in Inflammatory Rheumatism. MICHOTTE, L. J. (1960). *Rheumatism*, **16**, 11. 15 refs.

Other General Subjects

Rheumatism and Psoriasis. A Re-evaluation. WRIGHT, V. (1959). *Amer. J. Med.*, **27**, 454. 5 figs, 45 refs.

This paper from the General Infirmary at Leeds reviews the problem of the association of rheumatism and psoriasis with reference to a study of 154 patients with psoriasis and various rheumatic complaints. There

were no unusual features in either the skin or the rheumatic condition in 23 cases of osteo-arthritis, two of gout, two of rheumatic fever, and nine of muscular rheumatism, so that in these the association appeared to be quite fortuitous. The remaining 118 had psoriasis associated with erosive arthritis; 95 of these were compared with patients suffering from uncomplicated rheumatoid arthritis paired for sex, age of onset, and duration, and 85 with patients suffering from psoriasis alone, again paired for sex, age, and duration of disease.

These 118 patients fell into three distinct groups:

(1) 22 with arthritis involving primarily the distal interphalangeal joints and associated with nail changes;

(2) Ten with severe deforming arthritis, of whom four had typical arthritis mutilans;

(3) 86 with an arthritis indistinguishable clinically from rheumatoid arthritis.

In no case in Groups 1 and 2 was a positive reaction to the sheep-cell agglutination test obtained, whereas twenty patients in Group 3 gave a positive reaction and therefore were considered to be suffering from rheumatoid arthritis. The only nodules seen were found in these patients.

On the basis of the negative agglutination reaction as well as the clinical features of arthritis, the author suggests that psoriatic arthritis is an entity which may be of any of the three types described, and also that psoriasis and typical rheumatoid arthritis may not occur in the same patient. *B. M. Ansell.*

Intermittent Rheumatism. Palindromic Rheumatism, Intermittent Hydrarthrosis, and Allergic Rheumatism. (Reumatismos intermitentes. Reumatismo palindrómico. Hidrartrosis intermitente. Reumatismo alérgico.) ROTÉS QUEROL, J., and LIENCE, E. (1959). *Rev. esp. Reum.*, **8**, 8. 47 refs.

The authors describe from the Faculty of Medicine Barcelona, the cases of four patients with palindromic rheumatism, six with intermittent hydrarthrosis, and two in which the condition corresponded to the description of "allergic rheumatism", these occurring among over 2,000 patients with various rheumatic diseases. Each of these three types of episodic arthritis is examined in detail and the relevant literature reviewed.

In the four cases of palindromic rheumatism, rapid, sometimes sudden, attacks occurred from three times a month to three times a year, and lasted at most 3 days, some being present for only a few hours. Usually only one joint was affected at a time, the proximal interphalangeal joints being most frequently involved, but any joint might be the site of an attack. Non-articular swelling was also seen in all four cases, this including a transient swelling of the palate which the authors considered might be "palindromic rheumatism of a mucosal cavity". One patient aged 84 had had the disease for 44 years without evidence of residual arthritis. The duration of the disease in the other three cases was 1, 2, and 9 years respectively.

In the six cases of intermittent hydrarthrosis, attacks affected one or both knees (but usually one at a time), and uncommonly other joints. Pain resulted from the distension by fluid and was relieved by aspiration of the joint. In one case the knees were involved alternately, causing considerable incapacity, while in another the arthritis followed a cyclic course, affecting the right knee, right hip, left knee, right ankle in that order, with strict regularity. Some patients enjoyed longer periods of complete remission. The periodicity of the attacks varied from 9 to 18 days, but was constant for each patient. Three cases eventually showed evidence of rheumatoid arthritis and two of ankylosing spondylitis (representative case histories are given in detail).

The two patients with "allergic rheumatism" had episodic pain or swelling of the joints associated with angioneurotic oedema of the skin and other evidence of allergy.

The elaborate laboratory findings are tabulated and the differential diagnosis and treatment briefly discussed.

Allan St. J. Dixon.

Ann. rheum. Dis. (1960), **19**, 197.

IMMUNOLOGICAL ASPECTS OF RHEUMATOID DISEASE: A REVIEW

BY

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(1) INTRODUCTION

The methods by which tissue damage may result from an immunological reaction are mostly obscure. In considering the immunological aspects of rheumatoid disease, we have, therefore, first summarized known immunological reactions. We have then considered those features of rheumatoid disease which could be interpreted as being based on similar reactions. Finally, we have discussed whether the parallel is sufficiently close to justify the acceptance of rheumatoid arthritis as an autoimmune reaction.

In the present state of knowledge of immunology, three qualitatively different types of basic response to specific antigenic stimuli are recognizable. These responses, which may occur either separately or together, are (1) the production of "classical" circulating precipitating antibody, (2) the production of circulating skin-sensitizing antibody (reagin), and (3) the tuberculin-type of delayed hypersensitivity, in which serum antibody is not involved.

(2) NATURE AND SOURCE OF ANTIBODY

It has been known for a long time that the circulating antibodies of immune serum are found in the globulin fraction. Purified antibody globulin appears to differ little from "normal" serum globulin with regard to molecular weight, iso-electric point, or other physico-chemical properties; by salting-out methods, or by zone-electrophoresis for example, the immunologically active serum proteins are usually found in the gamma-globulin fraction, and analysis of chemical structure has shown no differences, in the terminal amino-acid sequences at any rate, between immunologically active and inert gamma globulin (Porter, 1950). The gamma globulin fraction of serum, however, is heterogeneous, and includes both low molecular weight (about 160,000) and high molecular weight (1,000,000) globulins, which may be separated in the ultracentrifuge as fractions with differing Svedberg sedimentation constants. In man, the commoner molecular size for antibody globulin corresponds to a sedimentation constant (S_{20}) of 7 S, but antibody activity (*e.g.* cold agglutinins, complete rhesus antibodies) is also found in the 19 S (macro globulin) fraction (Campbell, Sturgeon, and Vinograd, 1955). Electrophoresis, too, reveals heterogeneity of gamma globulins, based on differing mobilities of the molecules in an electric field, so that faster moving ($\gamma 1$) and slower moving ($\gamma 2$) components are demonstrable.

Circulating antibody has classically been detected by reactions with antigen leading to precipitation, agglutination or lysis of particles or cells, or toxin neutralization. In each case, the observable reaction is secondary to the primary union of antigen with antibody, and is determined by the particulate or cellular nature of the antigen (agglutination), by alteration of its biological properties (neutralization of toxic or enzymatic effect), or by a gross alteration in the physical state (precipitation) of both antigen and antibody brought about by their union. The detection of antigen-antibody reactions by complement fixation depends upon the inhibition of a similar gross change (haemolysis) in the sensitized red-cells of the indicator system. Circulating antibodies, however, may give rise to no directly observable reaction, and methods of modifying either antigen or antibody so as to render their reactions visible have been extensively developed. Examples of this are Boyden's method of coating tanned, red cells with protein antigens rendering them agglutinable by antibody (Boyden, 1951), and Coombs's antiglobulin test (Coombs, Mourant, and Race, 1945) for the detection of "incomplete" antibodies; and many other ingenious methods, notably Coons's fluorescent antibody method (Coons and Kaplan, 1950), have been developed in recent years.

The second class of circulating antibody mentioned above includes the skin-sensitizing antibody encountered in hay-fever and other common allergies. This antibody differs from the classical precipitating type in that it is relatively labile at 56° C., is difficult or impossible to detect by *in vitro* tests, and has a greater tendency to become fixed to tissue cells. The sera of most people with hay-fever and asthma contain reagins of this character, which when injected into the skin of a normal recipient confer a localized change such that subsequent injection of the corresponding antigen into the site produces whealing and erythema comparable to that which occurs in the skin of the donor in response to the same antigen (the Prausnitz-Küstner reaction). Although there is a strong hereditary predisposition towards allergy and the production of the associated reagins, in serum sickness about 90 per cent. of all persons can produce a similar skin-sensitizing antibody with properties indistinguishable from reagin (Cooke and Spain, 1929).

While most of the identifiable fractions of the serum are produced in the liver, the production of gamma-globulin is mediated by mesenchymal cells, principally in the lymph nodes and spleen (see the review by McMaster, 1953). In experimental work, the route of administration of antigen has an important influence on the distribution of cells activated to produce antibody. Thus intravenous injection of antigen into rabbits leads to hyperplasia and antibody-producing activity in the cells of the red pulp of the spleen (Fagraeus, 1948), while the first result of intradermal inoculation (into the foot pad, for instance) is the production of antibody in the regional lymph nodes (McMaster, 1942). Using the fluorescent-antibody method to detect gamma-globulin in cells, Coons, Leduc, and Connolly (1955), and Ortega and Mellors (1957) have produced strong evidence in animals and man respectively to support the view that the plasma cell series in both splenic pulp and lymph nodes are important for gamma globulin production. White, Coons, and Connolly (1955) and Ortega and Mellors (1957) have also shown that in lymph nodes the "intrinsic" cells of the germinal centres are also apparently capable of gamma globulin production. In contrast, the conclusive demonstration of antibody in lymphocytes is lacking, although good evidence (*e.g.* Chase, 1951, 1953) has been brought to show that lymphocytes are concerned with transport of antibody or transfer of ability to make it. Dixon, Weigle, and Roberts (1957), for example, have shown that transfer of suspensions of lymph node cells from immune animals to irradiated recipients can give rise in the latter to secondary responses of serum antibody. The relationship between macrophages, lymphocytes, and plasma cells developmentally and histologically is still a matter for dispute; but at present it seems justifiable to adopt the view of Burnet (1959), based on the suggestions of Taliaferro (1949), that mesenchymal cells with the inherent power of globulin production may, under appropriate conditions, take the form of stem cell, macrophage, lymphocyte, or plasma cell.

(3) *In vivo* Immunological Reactions

Idiosyncrasy, infection, or other contact with antigen may lead to hypersensitive responses based on immunological reactions. In experimental animals, a number of effects may be produced by antigen-antibody reactions. These often closely resemble sensitivity states in man, and provide a basis for studying mechanisms of hypersensitivity.

(A) Anaphylaxis.—The intravenous injection of an antigen into an animal already producing the corresponding circulating antibody usually gives rise after a brief interval to a generalized anaphylactic reaction. The symptoms vary with the species observed but are due to the release, following antigen-antibody interaction, of pharmacologically active substances (for example, histamine and serotonin), which alter the permeability of capillaries, cause contraction of smooth muscle, and disturb clotting mechanisms. Although anaphylaxis is mediated by circulating antibody, passive transfer of immune serum to normal animals will not sensitize them anaphylactically to a challenging dose of antigen unless a sufficient time interval elapses between administration of antibody and antigen (Benacerraf and Kabat, 1949). *In vitro*, moreover, antigen will not release histamine from guinea-pig lung sensitized by incubation with appropriate rabbit antiserum unless this incubation period has been half an hour or more (Mongar and Schild, 1957). Globulin (at least from certain species) adsorbs on to tissues much more readily than, say, albumin (Humphrey, 1959), and it seems that such fixation of circulating antibody on to cell surfaces is probably necessary before union of antigen with antibody can give rise to significant pharmacological activity. This is consistent with observations that histamine and serotonin are probably liberated from mast cells (Riley and West, 1953) and platelets (Hardisty and Stacey, 1955). Union of antigen and antibody may, in addition, activate other, non-cellular, systems—the esterase activity of complement, for example, and the proteolytic enzymes of blood (Lepow, Ratnoff,

Rosen, and Pillemer, 1956; Ungar, 1953). The anaphylactic type of reaction is essentially, therefore, an immunologically induced transient pharmacological response and is modified considerably by antihistamine drugs.

(B) ARTHUS REACTION.—Circulating antibody, however, can give rise to another type of hypersensitivity—the Arthus reaction—which is slower in onset, and inflammatory in nature. If a depôt of antigen is introduced into the tissues of an immune animal (or conversely, if a depôt of antibody is passively introduced and antigen injected intravenously) then a state of affairs is created where there is a local excess of one reagent in the tissues, and of the other in the bloodstream. Their interaction in the vicinity of vascular tissue leads to the development of a cumulative rather than a transient reaction beginning within a few hours. This consists of the formation of thrombi of leucocytes and platelets in the small blood vessels in the area, often proceeding to localized infarction, with a characteristic vasculonecrotic reaction, and marked infiltration of polymorphonuclear cells. This Arthus reaction differs from the acute anaphylactic response in that (1) much more antibody is needed to give the minimum response, (2) antisera from species (*e.g.* horse) inert in passive transfer anaphylaxis tests may give positive Arthus reactions, and (3) only precipitating antibody is fully effective in the Arthus reaction. The latter, moreover, is unaffected by antihistamine drugs, but is much modified by steroids and salicylates. Some authors regard polyarteritis nodosa as an example of a generalized Arthus reaction (Waksman, 1959).

The Arthus reaction, unlike acute anaphylaxis, is principally a cellular response to antigen-antibody complexes, and Gell and Hinde (1954) have shown that in the active Arthus reaction there is a mononuclear cell infiltration underlying the acute inflammatory vasculo-necrotic damage, and particularly discernible in mild lesions obtained early in immunization. Both anaphylactic and Arthus hypersensitivity are dependent upon circulating (or fixed, but once circulating) antibody.

(C) DELAYED HYPERSENSITIVITY (TUBERCULIN-TYPE).—A third type of hypersensitivity exists in which the dermal reaction to injected antigen in a sensitive individual is delayed; after several hours a progressive inflammatory reaction slowly develops and is maximal at 24-48 hours. This delayed response may be observed with protein antigens following their intradermal injection, or with bacterial proteins following infection by the specific organism. The tuberculin reaction is a well known example. The characteristic features of the delayed response are (1) a predominance of mononuclear cells arranged in cuffs around the blood vessels at the site of the delayed skin reaction, (2) lack of transference of hypersensitivity to normal subjects by serum, and (3) successful transfer by cells from lymph nodes or buffy coat of sensitive individuals. Experimentally, Freund's oil-and-mycobacteria adjuvant (Freund, 1956) injected with antigens greatly enhances delayed hypersensitivity, presumably because the mononuclear histiocyte reaction evoked by mycobacteria favours this type of response to antigen. Pure delayed hypersensitivity in man or animals seldom occurs without accompanying circulating antibody, but recent work of Uhr, Salvin, and Pappenheimer (1957) has shown that, by using suitable immunizing techniques, delayed hypersensitivity to diphtheria toxoid may be obtained in man and guinea-pig without serum antibody being detected. These experiments, and the undoubted occurrence of delayed responses in agammaglobulinaemic patients (Good, Bridges, Zak, and Pappenheimer, 1959), underline the cellular nature of this hypersensitivity and its essential independence of circulating antibody.

(D) ISO-IMMUNITY.—The immunological responses considered so far have been those directed against frankly foreign antigens—that is to say antigens not intrinsically present in the body's own tissues. It is well known that individuals may react immunologically to tissues from other individuals even within the same species (iso-immunity). The blood group antigens (some of which occur in many tissues besides red cells) and their natural or immune iso-antibodies are an obvious example. The development or enhancement of iso-immunity by the body when it encounters incompatible red cell antigens (whether in transfusion or in pregnancy) is associated with manifestly harmful effects, attributable, it appears, entirely to the destructive action of circulating antibody on incompatible cells.

(*i*) *Homograft Reaction.*—There is another class of iso-immune reaction, however, which gives rise to equally striking biological effects, but which is mediated principally or exclusively by cellular responses to antigenic stimulation. The homograft reaction (see Medawar, 1958) is of this type. The transplantation of living tissue from one individual to another of the same species usually leads to destruction of the transplant within about a fort-

night. A second graft from the same—but not from a different—donor is rejected characteristically more rapidly. The immunological nature of this so-called homograft reaction is demonstrated by the fact that this reactivity may be transferred from the graft recipient to normal individuals by lymph node and spleen cells. If a foreign graft is implanted in a host, but protected by a porous membrane allowing the passage of plasma but not of cells the graft remains undamaged (Algire, Weaver, and Prehn, 1954). The reaction of the host's tissues around the graft which accompanies its rejection is chiefly an infiltration of mononuclear cells. Both the cellular accompaniment of graft rejection and its tempo are much modified by steroids (Krohn, 1954), though not by antihistamines. In all these respects, therefore, the homograft reaction closely resembles a delayed hypersensitive response of the tuberculin type. Recent work (Brent, 1959) has corroborated this view by showing that antigenic tissue extracts from guinea-pig donors of skin grafts give rise to typical delayed skin reactions in recipient guinea-pigs which have already rejected grafts from the same donors. Moreover, lymph node cells from these same recipients injected back into the skins of their respective graft-donors give rise to similar delayed reactions on re-encountering the specific donor antigens in this way.

(*ii*) *Specific Immune Tolerance*.—The existence of iso-immunity is due to antigenic differences between individuals of the same species. Where no antigenic differences exist, no immunological consequences arise, as successful grafting between identical twins demonstrates. How, then, can the immunologically responsive cells of the body distinguish between "self" components and "non-self"? The phenomenon of immunological tolerance (*vide infra*) shows that this ability is acquired during foetal life. Billingham, Brent, and Medawar (1956) have shown that the introduction of living homologous tissue cells into the embryo before its immunological defence mechanism has become functionally mature leads after birth to acceptance and tolerance of skin homografts from the original cell donor, which in untreated animals would be rejected. That this tolerance of foreign tissue represents a central failure of the mechanism of immunological response is shown by Billingham, Brent, and Medawar, as follows:

> If a CBA (inbred) strain mouse has been made tolerant of A-strain tissues by inoculation in foetal life with A-strain cells, then in adult life it will accept and carry an A-strain skin homograft. This graft can be readily destroyed and tolerance to A-strain tissue abolished by injecting the CBA-host with lymph node cells from a normal CBA mouse actively immunized against A-strain tissue.

This shows that a tolerant mouse can "adopt" the immune mechanisms elaborated in a genetically identical but non-tolerant mouse. Therefore, a tolerated homograft, as Medawar points out, survives because there is no reaction against it, not because any reaction is prevented from taking effect; it is treated by its host, in fact, as "self".

(E) AUTOIMMUNITY.—Recognition of, and tolerance to, self, are clearly necessary conditions to the avoidance of immunological responses involving self. Nevertheless, some body constituents may escape this recognition and tolerance. In lupus erythematosus, for example, serum factors very like antibodies, with specificity for nuclear and cytoplasmic components, are commonplace (Dameshek, 1958); and antibodies to thyroglobulin and other thyroid antigens are frequent in thyroid disease (Roitt and Doniach, 1959). In the experimental field, iso- and auto-antibodies to spermatozoa (Freund, Lipton, and Thompson, 1953), thyroid (Rose and Witebsky, 1956), and brain (Rivers, Sprunt, and Berry, 1933) have been demonstrated in association with corresponding lesions induced by injecting these antigens with or without Freund's adjuvant. It is clear, therefore, that the body may fail to establish tolerance under certain conditions, or that already established tolerance may be broken. Thus we may envisage, as Roitt and Doniach (1957) suggest, certain antigens such as thyroglobulin, which are normally not available to the antibody-forming cells in foetal life, and against which tolerance is therefore never established. If, for any reason, leakage of these antigens occurs so that they come in contact with immunologically competent cells, then a specific immunological response occurs, as to any foreign antigen. On the other hand, failure of tolerance may be due to the emergence of immunologically competent cells capable of mediating specific reactions with certain body antigens.

The autoimmune conditions exemplified above could arise following either of these events. The former, where the antigen is only formally "self" and could not previously have been encountered by the immune mechanism, requires no further explanation. The latter also exists, however, and we have evidence for the occurrence of antibody reacting with readily accessible antigens (in haemolytic anaemia, for example) which compels us to consider how the mechanism for recognizing self operates.

Antibody production can scarcely be a simple matter of antigen imprinting its character on certain cells and thereby enforcing production of gamma globulin molecules bearing a complementary pattern, since this could explain neither the lack of antigenicity of body components nor the existence of tolerance phenomena. The persistence of antibody production for many years after antigenic stimulation (*e.g.* after some virus infections) and the differences between secondary and primary responses are also inconsistent with this concept. Instead of attributing a direct "template" activity to antigen, we can instead postulate (Jerne, 1955) that the gamma globulins in plasma form a population carrying all the reaction sites needed to react with any antigenic determinant, except those already existing in accessible components of the body. Further, we may postulate (Burnet, 1959) the existence of multiple clones of globulin producing mesenchymal cells, each responsible for one type of antibody globulin, and that this type is genetically determined. Antigen making contact with a cell capable of producing corresponding antibody stimulates proliferation of that cell, giving rise to a clone of daughter cells all producing the same specific antibody.

In this way antigenic stimulation could produce a specific response without direct determination of antibody configuration by antigen—by a process of selection of antibody. There are two further postulates necessary to this theory of Burnet's; the first is that somatic mutation of the genetic material of the antibody-producing cell is sufficiently frequent to give rise to the wide variety of globulin patterns required; the second is that, during development in embryonic life, the antibody-forming cells should pass through a transient phase of vulnerability to antigen, so that contact with it would result in death of the cell. If potential antigens persisted in sufficient amount, their presence in tissue would eliminate all clones of cells with which they could react ("forbidden clones") and the non-antigenicity of body components would be achieved. This theory has been developed by Burnet (1959) from the hypothesis of Jerne (1955), with the object of providing a theoretical basis for autoimmunity. It postulates that autoimmunity can arise following somatic mutations in immunologically competent cells leading to the production of forbidden clones, and that owing to some anomaly, either mutational or environmental, the transient vulnerable stage of development does not occur, so that secondary stimulation leads to antibody production as in any other immunologically active clone.

While this clonal selection theory fits many of the facts of immunity, it is not readily susceptible to test. Nevertheless, it provides a working account of considerable value as a basis for investigation and research in the field of autoimmune disease.

(4) Reactions in Rheumatoid Disease, possibly Immunological in Origin

(A) Rheumatoid Factor.—Waaler (1940) and Rose, Ragan, Pearce, and Lipman (1948) independently discovered that the sera of the majority of patients with rheumatoid arthritis would agglutinate sheep cells sensitized with a subagglutinating dose of rabbit anti-sheep cell antiserum. As a result of the extensive work stimulated by these observations, it soon became clear that, for the purposes of the test, cells of many species could take the place of the sheep cells and that the rabbit antisera could be replaced by antisera of diverse animal origins. A multiplicity of modifications of the original test was subsequently developed to enhance its sensitivity (Ziff, 1957). Furthermore, fractionation of strongly-positive rheumatoid sera has demonstrated that the active principle, the rheumatoid factor, also has both the solubility and electrophoretic properties of a γ globulin. Ultracentrifugal analysis, however, shows that it belongs to the category of macroglobulins with a sedimentation coefficient (S_{20}) of 19 as compared to a sedimentation coefficient of 7 for the bulk of normal γ globulins (Franklin, Holman, Müller-Eberhard, and Kunkel, 1957a; Svartz, Carlson, Schlossmann, and Ehrenberg, 1958). In whole serum, however, each molecule of the rheumatoid factor exists in a loose combination with several molecules of 7 S γ globulin, forming a complex with sedimentation coefficient of 22 S (Franklin, Kunkel, Müller-Eberhard, and Holman, 1957b).

The further clarification of the Rose-Waaler reaction came from studies not only of the factor itself but of the material with which it reacts in positive tests, now referred to as the reactant. The precipitin reactions of rheumatoid sera reported by Epstein, Johnson, and Ragan (1956), and the ability of most rheumatoid sera to agglutinate inert particles such as latex (Singer and Plotz, 1956) or bentonite (Bozicevich, Bunim, Freund, and Ward, 1958) when coated with γ globulin (*e.g.* human F.II), afford strong evidence that the reactant is in fact a γ globulin.

The three outstanding problems concerning the rheumatoid factor that remain to be considered are:

(*i*) Is the rheumatoid factor an antibody and its reaction with γ globulin an antigen antibody reaction?

(*ii*) Is the reactant a normal γ globulin or must it first be altered in some special way?
(*iii*) What role, if any, does the factor play in the pathogenesis of the disease?

Although the majority of antibodies are γ globulins of the 7 S category, several antibodies are known, both natural and acquired, that belong to the 19 S group of γ globulins (Franklin and Kunkel, 1957). The antibody nature of the rheumatoid factor cannot, therefore, be excluded on the grounds of its high sedimentation coefficient. Similarly, although the majority of antigen antibody complexes are able to fix complement, the failure of the rheumatoid factor-reactant precipitate to do so does not prove the non-immune nature of the combination, since many authentic antigen antibody complexes are known which also lack this property. Even more characteristic of an antigen antibody reaction than complement fixation is the shape of the curve obtained when, in an antigen-antibody system, the amount of antibody precipitated is plotted against increasing amounts of antigen added. The decrease in the amount of precipitate obtained when the antigen is increased beyond that causing maximum precipitation is due, of course, to the solubility of antigen-antibody complexes in excess of antigen. The failure of the curve of precipitation between F.II and rheumatoid factor to conform to that of a typical antigen-antibody precipitation curve has been particularly stressed by Vaughan, Ellis, and Marshall (1958), and is undoubtedly a serious objection to the view that rheumatoid factor is an antibody to altered γ globulin. However, although the inhibition of precipitation in the region of antigen excess is a striking feature of most precipitin systems, it is sometimes small or even absent (Wilson and Miles, 1955a). That it should be absent in the present system is indeed not entirely unexpected. It is presumably the presence of multiple hydrophilic groups in a protein antigen that are responsible for the phenomenon of solubility of an immune precipitate in antigen excess (Wilson and Miles, 1955b), and with heat denatured F.II we are undoubtedly dealing with a protein that has already lost the major part of its hydrophilic property by virtue of the process of denaturation.

Finally, antibody globulins are largely, if not exclusively, produced by plasma cells, and their presence can be clearly revealed by the use of fluorescent antibody applied to histological preparations pretreated with antigen. Mellors, Heimer, Corcos, and Korngold (1959), by applying this method and using heat-aggregated γ globulin as the antigen, have clearly demonstrated that rheumatoid factor like true immune globulins is found in typical plasma cells.

Largely because of the work of Kunkel and his colleagues, it is generally held that the reaction between the rheumatoid factor and reactant requires no specific change in the latter, and this view is supported by the observation that in whole serum the factor exists as a complex with presumably normal 7 S γ globulin. Kunkel's own observation, that the Epstein precipitin reaction is greatly increased by heating the reactant to 63° C. for 10 minutes, is interpreted as indicating nothing more than that the heat aggregated material is more readily precipitable than the non-aggregated material. If this be true, however, it is difficult to see why, for example, the rheumatoid factor which in whole serum is already bound to 7 S γ globulin should exchange this for γ globulin aggregated by heat or specifically absorbed on to an antigenic surface as in the sensitized sheep cell test. That such an exchange does actually take place has been elegantly shown by Christian (1959). He found that, when rheumatoid factor of 22 S separated by ultracentrifugation is made to precipitate with 7 S γ globulin previously aggregated by heat, the 7 S fraction originally bound to the 19 S fraction is progressively liberated into the supernatant as more of the heat-aggregated globulin is added.

A technical modification known as the inhibitor test was introduced by Ziff, Brown, Lospalluto, Badin, and McEwen (1956). The basis of this test is the presence in normal serum of a factor capable of inhibiting the agglutination of sensitized sheep cells by rheumatoid sera and the absence of this factor from the serum of patients with rheumatoid arthritis. It was claimed for this test that rheumatoid sera too weak in the rheumatoid factor to give a positive agglutination titre with sensitized cells could still be detected because of the absence of inhibitor. Undoubtedly by this means a considerable increase of sensitivity was attained. Unfortunately, in the hands of most other investigators, this was matched by a corresponding fall in specificity. Recently a similar modification of the latex particle agglutination test has been introduced (Dresner and Trombly, 1959), which is also based on the absence of inhibitor from rheumatoid sera, and shows a comparable gain in sensitivity and loss of specificity. A study of the patients that gave a false positive reaction with this test, however, showed that the great majority were suffering from a virus infection, syphilis, or some hepatic disease, *i.e.* from conditions which usually offer little confusion with rheumatoid arthritis. A positive latex-inhibition test, therefore, in a patient from whom

these diseases can be excluded is indicative of rheumatoid arthritis with a probability of almost 100 per cent.

Since reactant γ globulin may be obtained from a wide variety of animal species, it is necessary to postulate a high degree of non-specificity in the reaction with rheumatoid sera, and, since immunological specificity of a protein is largely determined by its tertiary configuration, *i.e.* the coiling of the helical peptide chains, the most economical hypothesis to explain these facts is that advanced by us in 1957 (Glynn, Holborow, and Johnson, 1957). We then suggested that the rheumatoid factor is an antibody specifically directed against antigenic groups shared by many species of γ globulin and exposed when the native proteins become unfolded either by heat, or by specific interaction with an antigenic surface, or on non-specific adsorption by certain non-antigenic surfaces such as latex or bentonite.

Since some degree of denaturation of γ globulin must be a frequent occurrence both in man and animals, the antigenic activity of such denatured globulin must be presumed to be enhanced in rheumatoid subjects. In other words, according to our hypothesis, the presence of rheumatoid factor in any individual implies the ability of the immune mechanisms of that individual to recognize as foreign the altered autogenous γ globulin, whilst normal individuals without rheumatoid factor lack this ability. That is to say that the rheumatoid subject is apparently capable of recognizing, and therefore regarding as foreign, a degree of change in an autogenous protein that is ignored by the immunological mechanism of normal individuals.

The Gm groups described by Grubb (1958) appear to support this conclusion, although he himself does not regard the rheumatoid factor as an antibody. Briefly, if human Group O Rhesus D positive cells are sensitized with certain human sera containing incomplete anti-D, they can be agglutinated by some rheumatoid sera. Human sera can then be divided into two groups according to their ability, or inability, to inhibit this system. The inhibitory sera are designated Gm a+, the non-inhibitory Gm a−. The inhibitory activity in the Gm a+ sera has been shown to be present in the γ globulin fraction. If the agglutination of the sensitized D-positive cells is indeed an immunological reaction, it is apparent that certain rheumatoid sera, themselves either Gm a+ or −, can distinguish two genetically determined varieties of human γ globulin.

The role of the rheumatoid factor in pathogenesis is difficult to assess. There is no strong correlation between the amount of factor and clinical severity, but a positive correlation has been established with the duration of the disease and especially with the presence of subcutaneous nodules (Ball, 1952; Jacobson, Kammerer, Wolf, Epstein, and Heller, 1956). Attempts to demonstrate a pathogenic effect of the factor by administration of high titre sera (Vaughan and Harris, 1959) or an ameliorating effect by sera rich in inhibitory factor have been uniformly unsuccessful (Ziff and others, 1956). Neither of these experiments should be taken as convincing evidence that the factor is without pathogenic effect, since the quantitative differences between passive administration and active formation must be considerable.

(B) L.E.-Cell Phenomenon, and Anti-nuclear and Anti-cytoplasmic Factors.—A second serum factor of immunological significance found in some cases of rheumatoid arthritis is that responsible for the L.E. cell phenomenon, first described by Hargraves, Richmond, and Morton (1948) in cases of disseminated lupus erythematosus. In that disease many patients possess in their serum a γ globulin of the 7 S variety that is capable of inducing the nuclear changes and phagocytosis that result in the typical L.E. cell (Haserick and Bortz, 1949). The incidence of this substance in cases of rheumatoid arthritis varies considerably with the technique used for its demonstration, but it is variously estimated as between one (Ishmael, 1955) and 17 per cent. (Kievits, Goslings, Schuit, and Hijmans, 1956). In disseminated lupus erythematosus and in rheumatoid arthritis, the presence of the L.E.-cell factor is usually associated with other γ globulins capable of reacting with various nuclear constituents but nevertheless incapable themselves of inducing the formation of typical L.E. cells (Robbins, Holman, Deicher, and Kunkel, 1957). These interactions include precipitation and complement fixation with desoxyribonucleoprotein or desoxyribonucleic acid. The presence of these various proteins in the 7 S γ globulins, the fixation of complement and the shape of the various precipitin curves (Deicher, Holman, and Kunkel, 1959) leave little doubt that these various factors must be regarded as true antibodies and their reactants as antigens or haptens. With regard to the L.E.-cell phenomenon itself, the nature of the reactant is presumably DNA histone, since the factor can only be absorbed by whole nuclei or native DNA histone (Hijmans and Schuit, 1958), but not by DNA or free histone. Until recently the change undergone by the phagocytosed nucleus in typical L.E. cells was regarded as a depoly-

merization of its desoxyribonucleoprotein. This view was based upon the weakness of its staining with methyl green relative to the strength of the Feulgen reaction. The work of Godman and Deitch (1957), however, has clearly shown that the weakness of the staining with methyl green is not due to depolymerization but to substitution of histone by some other protein more firmly bound to the DNA. Normally, staining with methyl green is apparently brought about by displacement of histone by the dye. In the L.E. cell the weakly-bound histone is partly displaced by other proteins more firmly bound. It seems highly probable, although not yet proven, that this firmly bound protein is the L.E.-cell factor itself.

A phenomenon related to that of the L.E. cell and described by Friou, Finch, and Detre (1958) and by Holborow, Weir, and Johnson (1957) is the ability of L.E. sera and some rheumatoid sera to react with nuclei in tissue sections, the reaction being subsequently revealed by staining with a fluorescent rabbit anti-human γ globulin antiserum. The failure of this so-called anti-nuclear factor to react with guinea-pig spermatozoa, although reacting strongly with the spermatogonia and spermatids, suggests that histone plays some essential role (Holborow and Weir, 1959). Since the anti-nuclear factor does not react with either DNA or histone when free, nor with nucleo-proteins consisting of DNA and protamine, it has been suggested that the reactant is histone but only when a specific configuration has been impressed upon it by its union with DNA (Editorial, 1959). This view receives support from the observation that the DNA can be removed enzymatically from nuclei pretreated with anti-nuclear factor without impairing the subsequent staining by fluorescent anti-globulin (Holborow, 1960). Reactions capable of fixing complement have not only been described between serum proteins and nuclear constituents but also, although less frequently, with cytoplasmic constituents. These include mitochondria, microsomes, and soluble cellular protein (Asherson, 1960). As with the nuclear reactions, the majority of patients giving these cytoplasmic reactions are suffering from disseminated lupus erythematosus.

(C) Haemolytic Anaemia and Leucopenia.—The two serum factors considered above do not appear to be directly responsible for any of the known lesions of rheumatoid arthritis. On the other hand, there are several lesions commonly found in this disease for which there is a strong possibility that circulating antibodies play an important causative role despite the difficulty usually encountered in demonstrating their presence. For example, leucopenia is common in rheumatoid arthritis and on some occasions has been associated with apparently specific antibodies, detected by a Coombs consumption test (van Loghem, van der Hart, Hijmans, and Schuit, 1958).

Anaemia, also a common finding in rheumatoid arthritics, has not yet been shown to be associated with an autoimmune mechanism, but its many clinical features (McCrea, 1957) strongly suggest the participation of an underlying autoimmunity. The frequency with which leucopenia, anaemia, and thrombocytopenia occur in disseminated lupus erythematosus associated with specific autoantibodies suggests that a similar mechanism may well underlie these same phenomena in rheumatoid arthritis.

(D) Vascular Lesions.—The incidence and significance of the vascular lesions in rheumatoid arthritis has received considerable attention in recent years. A question of major clinical significance is the role of corticosteroid therapy in the apparent increase in the incidence of arteritis (Kemper, Baggenstoss, and Slocumb, 1957). Since comparable vascular lesions undoubtedly occurred in rheumatoid arthritis before the era of corticosteroid therapy, the lesions cannot be regarded as exclusively iatrogenic. The effective use of corticosteroids in suppressing immunological reactions and their apparent failure to influence favourably the arteritis of rheumatoid arthritis could be regarded as evidence against an immune pathogenesis of the vascular damage. The corticosteroids, however, have profound metabolic effects quite apart from those they exert on immunity. For example, the adverse effects of hypertension resulting from the corticosteroids might well outweigh any advantages obtained from their immunological effects. The ready production of an acute necrotizing arteritis in experimental animals by immunological methods, such as the repeated injection of foreign serum (Rich and Gregory, 1943), and the finding of similar lesions in man in comparable circumstances (Rich, 1942) certainly encourages the view that the vascular lesions of rheumatoid arthritis have a similar immune pathogenesis. Here it is perhaps important to differentiate two types of immunological reaction that can be used to produce an experimental vasculitis. With the most commonly practised experimental method, namely the intravenous injection of large amounts of foreign antigen, the lesion is apparently the result of the interaction of antigen and antibody within the vessel wall. It has, however, proved possible to produce vas-

cular lesions by the injection of sera containing specific antibodies to antigens naturally present in the particular vessels in question, *e.g.* the injection into guinea-pigs of an anti-Forssman antibody prepared, say, in rabbits (Tanaka and Leduc, 1956). Although in rheumatoid disease either of these two mechanisms seems possible, there is not at present any convincing evidence of specific anti-vascular antibodies in human subjects. It is, however, conceivable that the interaction of the rheumatoid factor with its reactant could take place in the vessel wall in the same way as specific antibody and foreign serum antigens interact in the experimental animal.

(E) SJÖGREN'S SYNDROME.—Yet another clinical feature shown by a significant proportion of rheumatoid arthritics for which an immunological basis has recently been suggested is the dryness of the mouth and grittiness of the eyes now usually referred to as Sjögren's syndrome. In this condition the lacrimal and salivary glands show atrophic changes of the parenchyma accompanied by a variable degree of cellular infiltration consisting mainly of plasma cells and lymphocytes. The similarity of the histological picture to that of the thyroid in Hashimoto's disease was indeed commented upon some years before the immunological features of this disease had been recognized (Cardell and Gurling, 1954). It must be admitted that at present the evidence in favour of an immunological pathogenesis is suggestive rather than convincing. Jones (1958) studied sera for the presence of precipitins by immuno-diffusion against an extract of lacrimal gland, and found only one clearly positive. To account for the high proportion of negative results, however, it was pointed out that these were all from cases of long standing, in which presumably the complete destruction of the gland had led to the loss of any further antigenic stimulation, and hence to the disappearance from the serum of demonstrable antibody. Heaton (1959) has recently reported the finding of L.E. factor in the serum of ten cases of Sjögren's syndrome out of 28 studied. In the absence of the criteria used for the recognition of an L.E. cell, it is impossible to assess the significance of this observation, and in view of the incidence of the L.E.-cell phenomenon in rheumatoid arthritis cannot be accepted as proof that Sjögren's syndrome is a feature of disseminated lupus erythematosus. Attempts by us to demonstrate a circulating antibody in the serum of four patients with the syndrome by means of the Coon's sandwich technique have been unsuccessful. It is evident that conclusive evidence of the immune pathogenesis of Sjögren's syndrome is still lacking.

(F) SUBCUTANEOUS NODULES.—The subcutaneous nodules so characteristic of rheumatoid arthritis have much in common histologically with the granulomata of other specific diseases such as tuberculosis and syphilis. To what extent the infective granulomata owe their characteristic features to an immunological reaction to the causative agents is still a moot point, but until recently there was little evidence implicating immunological participation in the development of the rheumatoid nodule, despite the demonstration, by immuno-fluorescent staining, of the presence within the nodule of γ globulin (Vazquez and Dixon, 1957), and the positive correlation between the presence of nodules and the rheumatoid factor in the serum. Evidence more suggestive of an underlying immunological abnormality has been adduced by Banerjee and Glynn (1960) from a study of the reactions of experimental animals to implants of fibrin from their own or other species. With homologous fibrin, invasion by fibroblasts and capillaries was rapid, and within 2 to 4 weeks, depending upon the size of the implant, the fibrin was completely replaced by a small fibrous scar. With heterologous fibrin implants, the reaction was similar to that with homologous fibrin for the first 5 to 7 days. From then on the difference was striking: the fibroblasts that had penetrated the fibrin underwent necrosis, whilst those at the periphery arranged themselves at right-angles to the surface of the implant to form a palisade strikingly reminiscent of that seen in a rheumatoid nodule. The peripheral vascular formations, with their associated infiltrations of lymphocytes, histiocytes, and plasma cells, contributed to the remarkable similarity between the experimental lesion and a typical rheumatoid nodule.

Several features of the reaction to the foreign fibrin implants suggested that the differences from the reaction to homologous fibrin were due to the antigenicity of the foreign fibrin. Thus the latent period between the time of implantation and the appearance of the characteristic reaction is presumably required for the stimulation and reaction of the immune mechanisms of the host. Plasma cells, known to be associated with immune reactions and engaged in the synthesis of specific antibodies were conspicuous in the host tissues in the vicinity of the implant and indeed circulating antibody against fibrinogen of the donor species could be demonstrated. Furthermore, the repetition of the implant some weeks after a primary implantation leads to an

accelerated response, and finally such an accelerated reaction may show an acute necrotizing arteritis similar to that produced by massive injections of foreign serum.

It is, of course, at this stage impossible to say to what extent the similarity between the natural and the experimental "nodules" are due to similarities in their pathogenesis. The presence of γ globulin in the rheumatoid nodule and the correlation between the presence of nodules and rheumatoid factor in the serum do, however, encourage the view that the similarities will not prove entirely fortuitous.

(5) Discussion

Despite the growing volume of evidence implicating disturbances of immune mechanisms in the pathogenesis of the rheumatoid diseases, the recent observation of the frequency of these diseases among patients with congenital agammaglobulinaemia (Gitlin, Janeway, Apt, and Craig, 1959) has shown that circulating antibody and indeed the plasma cells that give rise to it cannot play the fundamental pathogenetic role. It must, however, be realized that, even in congenital agammaglobulinaemia, the absence of γ globulins is rarely absolute and the use of sensitive immunological tests usually reveals small amounts to be present. Furthermore, antibodies are not confined exclusively to this group of proteins. Several occur in both the α and β fractions (Cann, 1959). Finally, several incontrovertibly immune reactions, *e.g.* the tuberculin reaction, are unrelated to the presence of circulating antibody and cannot in consequence be transferred passively by serum proteins. On the contrary, they are mediated by certain cells of the lympho-reticular system and can be readily transferred passively by the cells of this system. It is probable, therefore, that if an immune mechanism underlies the development of rheumatoid disease it is a mechanism more akin to that responsible for the delayed, than for the immediate, type of hypersensitivity. The extensive production of experimental lesions of the brain (Kabat, Wolf, and Bezer, 1947), thyroid (Witebsky and Rose, 1956), testis (Freund and others, 1953), and adrenal (Colover and Glynn, 1958), by what appear to be autoimmune mechanisms has produced results in harmony with this view. In each of these examples the actual damage is apparently mediated by cells and not by circulating antibody. Even in those experimental animals in which a circulating antibody can be demonstrated, it has never been shown that the antibody is responsible for the lesions, and on some occasions at least it has been suspected that these circulating antibodies might even exert a protective function (Florey, cited by Vulpé, 1959). In this group of experimental diseases the mechanism is therefore more akin to the delayed type of reaction. It differs, however, from the tuberculin reaction in that the appropriate lesions cannot be induced by a simple transference of lymphocytes from affected to normal animals. The difference, however, is not fundamental but presumably due to the necessary survival period of the transferred cells. With transference of tuberculin sensitivity, survival of the transferred cells is not necessary. With transference of experimental allergic encephalitis, however, the importance of adequate survival of the transferred cells has been clearly shown by Paterson (1960). He had found, in accordance with other workers, that the transfer of a suspension of lymph node cells from a donor with experimental allergic encephalitis to a recipient even of the same strain did not result in the transfer of the disease. If, however, the recipient had been rendered tolerant of the donor's cells by a cell transfer from the donor at about the time of birth of the recipient, transfer of the allergic encephalitis could be successfully achieved.

It is now well over a decade since the possibility that rheumatoid arthritis is an autoimmune disease has been seriously considered. The evidence in favour of it, and largely acquired during that period, falls into two groups:

(1) Certain properties of the serum are strongly suggestive of the presence of an antibody capable of reacting with host antigens such as aggregated γ globulin or various nuclear and cytoplasmic components;

(2) Some of the lesions of rheumatoid arthritis have much in common with experimental lesions induced by immunological procedures. These include the arteritis and nodule formation. Furthermore, the plasma cell, now generally accepted as the main source of immune γ globulin, is the characteristic cell of the histology of rheumatoid lesions.

It is apparent from the available evidence that the hypothesis that rheumatoid arthritis is an autoimmune disease is still far from proven. The only convincing proof would be the transference of the disease by living lymph node cells to a recipient tolerant to these, *i.e.* the human equivalent of Patterson's method for the transmission of allergic encephalitis in guinea-pigs. Even if ethically justifiable, such an experiment could at present only be performed with identical twins. Assuming, however, a successful outcome of such an experiment, we should still lack the fundamental know-

ledge how and why this basic change had occurred in the immunological mechanism of the rheumatoid patient. Until we pass from the phase of speculation to the phase of facts concerning immunological tolerance and the recognition of self, we shall remain unable to understand the nature of that fundamental disturbance that must underlie all diseases of an autoimmune kind, namely the breakdown of the mechanism of self recognition. An essential prerequisite for such an understanding is of course the elucidation of the means by which cells with the potential for antibody production normally avoid the elaboration of autoantibodies. It is conceivable that common to all the possible antigens in any individual is a unique self-marker, which is in some way responsible for the failure of immune response by cells of the same individual, themselves endowed with the same self-marker. Simpler to comprehend is the view recently put forward by Burnet (1957) that accounts for the normal absence of autoimmune reactions not by self-markers but by the elimination during foetal or early post-natal life of those cells capable of reacting with self antigens. The reappearance of such cells in patients with autoimmune disease is accounted for by a somatic mutation of some of the cells of the antibody forming system. Such mutations are an essential feature of Burnet's hypothesis and the appearance of cells capable of forming autoantibodies should therefore be a common occurrence. The rarity of the diseases attributable to autoimmunity therefore requires a homeostatic mechanism for the elimination of such undesirable mutants. According to this hypothesis, therefore, the development of autoimmunity results from the breakdown of this homeostatic mechanism.

Although, therefore, the role of autoimmunity in the pathogenesis of rheumatoid disease must still be regarded as hypothetical, the stimulus that this concept has provided has been immeasurable and the features of the disease discussed above are not without encouragement to the proponents of the autoimmune hypothesis.

Summary

The various immunological reactions reproducible experimentally in animals or man have been discussed. These include anaphylaxis, the Arthus reaction, delayed hypersensitivity of the tuberculin type, and the homograft reactions. Lesions (*e.g.* the subcutaneous nodule) and serological reactions (*e.g.* the Rose-Waaler test) are then considered in the light of these known immunological reactions, from which it is concluded that autoimmune phenomena are probably of significance in the pathogenesis of rheumatoid disease.

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Aspects immunologiques de la maladie rhumatismale

RÉSUMÉ

On considère les différentes réactions immunologiques que l'on peut reproduire expérimentalement chez l'homme ou l'animal. Celles-ci comprennent l'anaphylaxie, la réaction d'Arthus, l'hypersensibilité du type provoqué par la tuberculine et les réactions à la greffe homologue. Par rapport à ces réactions immunologiques connues, on considère certaines lesions (telles que nodules souscutanés) et certaines réactions sérologiques (telles que celle de Rose-Waaler), et on conclue que les phénomènes d'autoimmunisation jouent probablement un rôle dans la pathogénie de la maladie rhumatismale.

Aspectos imunológicos de la enfermedad reumatoide

SUMARIO

Se consideran las diferentes reacciones imunológicas reproducibles experimentalmente en los animales o en el hombre. Estas incluyen anafilaxia, reacción de Arthus, hipersensibilidad retardada del tipo de la porovocada por la tuberculina, y reacciones a los homoinjertos. En comparación con estas conocidas reacciones imunológicas se consideran ciertas lesiones (tales como los nódulos subcutáneos) y ciertas reacciones serológicas (tales como la de Rose-Waaler). De dicho análisis se concluye que los fenómenos de autoimunización tienen probablemente cierta importancia en la patogenia de la enfermedad reumatoide.

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"RHEUMATOID ARTHRITIS" WITH NEGATIVE SEROLOGICAL REACTION

BY

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This paper describes a follow-up study of in-patients with severe active rheumatoid polyarthritis, in whom the sensitized sheep cell agglutination test (S.C.A.T., Ball, 1950) was found to be negative.

Patients

The patients reviewed in this study comprise all those treated as in-patients in the rheumatism beds of the Manchester Royal Infirmary during the period 1948 to 1956 inclusive, who were sero-negative, but in whom, during their first admission, no diagnosis other than rheumatoid arthritis or polyarthritis of undetermined type could be made by the accepted criteria (Ropes, Bennett, Cobb, Jacox, and Jessar, 1956). An erythrocyte sedimentation rate of over 20 mm./hr (Westergren) was also required as a criterion of disease activity. 63 patients conformed to this definition and these were selected for follow-up. This number represents some 6 per cent. of all the patients admitted to the rheumatism beds during these years. While the patients were in hospital the S.C.A.T. was done weekly; some tests were also done at subsequent out-patient attendances, but in all cases the test was repeated at the follow-up examination.

Serological Criteria

For this study it was desirable to eliminate borderline results in the test so that a negative test was defined as one in which no agglutination was observed after incubation for 18 hrs with serum dilutions greater than 1 : 8. This criterion for a negative test is more strict than that described in previous publications from this Centre, in which agglutination with a titre of 1 : 32 is accepted as a minimal positive result (Kellgren and Ball, 1959). Great care has been taken to maintain standard sensitivity of the test over the years, and all new batches of reagents are adjusted to give standard results with arbitrary standard sera. Control sera of known titre are tested with each batch of unknown sera, and the whole batch is retested or rejected if the controls are unsatisfactory. Control sera are stable for at least a year. Thus changes in the S.C.A.T. observed at follow-up may be regarded as real and not "technical".

This study group of patients was tested frequently. So that the results of all available tests could be taken into account, those patients in whom not more than one borderline titre of 1 : 16 was found amongst at least four negative tests within any 6 months' period were included as sero-negative and were not excluded from the follow-up series, but if more than 25 per cent. of the readings during any 6 months were 1 : 16 or more, the case was excluded from follow-up. In the remainder of this paper, the convention of reciprocal titre will be observed. Thus a S.C.A.T. of less than 4, 4, or 8 is negative, of 32, 64, etc., positive, and of 16 "doubtful positive".

Diagnostic Criteria and Predictability of the S.C.A.T.

In typical, sero-positive nodular rheumatoid arthritis, the disease may start in many ways, and the pattern of joint involvement at onset may differ from that seen later. Nevertheless, it has been shown that in hospital in-patients with polyarthritis the results of the S.C.A.T. can be predicted from the clinical and radiological features of the case with considerable accuracy (Kellgren and Ball, 1959) and as a result of this the clinical features of fully-developed sero-positive rheumatoid arthritis have become more clearly defined. Typical rheumatoid arthritis showed symmetrical peripheral polyarthritis, including (as a minimum) involvement of both wrists, the second and third metacarpophalangeal joints of both hands, and the lateral metatarsophalangeal joints in the feet. In the more

developed case, of course, this extended to involve all the small joints of the hands and feet as well as the larger limb joints. Atypical arthritis was diagnosed when mainly central, large joint, or asymmetrical involvement was seen. In practice the distinction was seldom difficult. Radiological evidence of subchondral and juxta-articular erosions was helpful in assessing the extent and distribution of joint involvement.

Follow-up Procedure

All patients were recalled for a review of the history and a fuller examination. Nodules were sought over bony prominences, under the heels, and in the finger flexor tendons. Only moderate or large flexor tendon nodules were considered significant. Blood was taken for S.C.A.T., E.S.R. (Westergren), Hb per cent., and serum urate estimations (Brown, 1945). Further radiographs were taken where indicated and all previous films were reviewed.

Results

Tables I and II show that the follow-up was reasonably complete and that nearly half of the patients were observed for 5 years or more.

TABLE I

COMPLETENESS OF FOLLOW-UP

Follow-up		No.	Per cent.
Total patients chosen for follow-up		63	100
Seen again as out-patients or in-patients ..		50	79
Died in interval		6	10
Follow-up by letter only		5	8
Failed follow-up	Not traced 1	2	3
	Traced but did not reply 1		

TABLE II

INTERVAL BETWEEN HOSPITAL ADMISSION AND FOLLOW-UP OR DEATH

Interval (yrs)	10	9	8	7	6	5	4	3	2	1	Total
No. of Patients	1	5	2	8	6	7	5	6	14	7	61

The findings at follow-up are summarized in Table III. Twelve patients became sero-positive. This includes all of the six patients who developed persistent subcutaneous nodules. In ten of this group the arthritis was typical in distribution, and in these cases either flexor tendon nodules and/or subcutaneous nodules were present at follow-up.

TABLE III

CLINICAL FINDINGS IN RELATION TO S.C.A.T., AS DETERMINED AT FOLLOW-UP OR DEATH

Clinical Findings	S.C.A.T. Titres			
	1:32 or More	1:16	1:8 or Less	Total
Typical Rheumatoid Arthritis	9	1	Alive 21, Dead 3 } 24	Alive 31, Dead 3 } 34
Atypical Rheumatoid Arthritis (All Alive) ..	1	1	9	11
Other Arthritides ..	0	0	Alive 8, Dead 3 } 11	Alive 8, Dead 3 } 11
Total	10	2	44	56

The duration from the onset of disease to the development of sero-positivity can be approximated from Table IV, which shows that this process may take at least 15 years and possibly even longer in some cases.

TABLE IV

DURATION OF ARTHRITIS BEFORE S.C.A.T. CONVERSION (YRS)

Duration from Onset of Arthritis ..		To Last Recorded Negative S.C.A.T.	To First Recorded Positive S.C.A.T.
(A) Typical Arthritis	N.W.	3	5(1:16)
	E.C. (Case 28)	2	6
	M.H. (Case 26)	9	15
	U.W. (Case 2)	15	23
	N.W.	10	12
	D.S. (Case 1)	2	8
	J.R. (Case 17)	6	13
	M.R.	2	5
	I.L.	1	2
	E.H. (Case 4)	7	14
(B) Atypical Arthritis	K.D. (Case 3)	13	14(1:16)
	J.H.	4	6

In only one patient who eventually developed typical arthritis and a positive serology was the arthritis observed to be atypical for a major proportion of the course of the disease.

Case 1, a man aged 55, had pain in the left shoulder in 1949. Both knees and both wrists were involved later that year, and the neck and metacarpophalangeal joint of one thumb the following year. He was seen regularly in hospital, but a typical distribution of involvement of the metacarpophalangeal and proximal interphalangeal joints was not observed until 5 years after onset. Typical subcutaneous nodules appeared about the same time. His subsequent course showed steady deterioration.

Another patient in this group is of interest.

Case 2, a woman aged 34, had developed arthritis in the right shoulder, and this had spread to involve all the large limb joints except the hips. Ten courses of gold treatment were given with diminishing success over the next 10 years. After 9 years her fingers became involved. After 10 years nodules were removed from both elbows, and 5 years later she attended hospital with typical active advanced rheumatoid arthritis (E.S.R. 82 mm./hr) and established deformities of the hands and feet. Her thumbs were disorganized at the interphalangeal joints, and these joints were surgically arthrodesed. Histological examination (Dr. J. Ball) of the tissue removed at surgical arthrodesis of the thumbs showed dense fibrous tissue containing an old necrobiotic focus and areas of active inflammatory proliferation and infiltration. Three estimations of the S.C.A.T. were 4, <4, and <4 respectively. 8 years later, at follow-up, when she was aged 66, further subcutaneous nodules had appeared, and her appearance was that of "arthritis mutilans".

The S.C.A.T. was then positive (128).

One patient developed a S.C.A.T. of 16 (doubtful positive) whilst her arthritis was considered to be atypical.

Case 3, a woman aged 38, began to have intermittent hydrarthrosis of the left knee when aged 24. The attacks were regular but not disabling until the age of 33, when both knees began to swell intermittently, with residual permanent swelling from the age of 36. Persistent arthritis of the right wrist started at age 36 and of the right shoulder at age 37. Small heel nodules were noted on examination at age 38. Five estimations of the S.C.A.T. at age 37 were negative (8, 8, 4, 8, 8), but at follow-up one year later the titre had risen to 16.

Comment.—The majority of those who became sero-positive showed a typical arthritis from an early phase of the disease, but an interval of up to 15 years might elapse before serological conversion was observed to occur, and this is relevant to the evaluation of the remaining patients in this study, in the majority of whom sero-conversion did not occur, and who had not been followed for as long as this. In Case 2, sero-negativity for many years was compatible with presence in the body of extensive synovial disease, histologically similar to, if not indistinguishable from, the appearance of subcutaneous nodules.

Sero-negative Group with Typical Distribution of Arthritis.—Of the 24 patients in this group, only one had shown transient subcutaneous nodules, and eight (including three of those who had died) showed no nodules of any sort, but there remained twelve who were noted to have significant flexor tendon nodules. In ten of these twelve, radiographs revealed evidence of articular bone erosion. Comparison of these 24 patients with the ten who had typical arthritis and who became sero-positive revealed no other notable differences, either in course or outcome. Both mild and severe end-results were seen. In one patient inflammatory polyarthritis was very severe indeed and was the cause of death.

Case 4, a woman aged 50, injured her right index finger, which became swollen, stiff, and painful. After 6 months, swelling spread to her knees and most other joints. There was much constitutional illness and loss of weight. When seen at the age of 52 she was wasted and ill, with enlargement of the lymph nodes. All joints were involved, but the smaller peripheral joints were especially swollen, tender, limited, and in many cases subluxed. There was slight fever (to 99·6° F.), anaemia (haemoglobin 50 to 68 per cent.), and reversal of the serum protein ratio (albumin 2·6 g. per cent.; globulin 3·7 g. per cent.). A chest radiograph was normal. All treatment was unsuccessful.

At the age of 54 the patient died, and at autopsy (Dr. Ball) showed gross deforming rheumatoid arthritis; the histology was that of an extensive erosive arthropathy without ligamentous calcification, affecting especially the small joints, although all joints (including the sacro-iliac, lumbar interfacetal, and sternoclavicular) were involved. The condition was entirely compatible with rheumatoid arthritis. Five estimations of the S.C.A.T. had all been negative (4 or <4). Pulmonary tuberculosis was also found, but was histologically a terminal infection, an opinion supported by a shortly previous normal chest *x* ray.

Other patients in this group have fared better.

Case 5, a woman aged 58, developed general illness, loss of weight, and swelling and stiffness of the hands. By age 59 she had symmetrical involvement of the proximal interphalangeal joints and metacarpophalangeal joints, especially the first and second on each hand, and there was involvement of wrists, elbows, shoulders, neck, knees, ankles, and feet, with pain and limitation of movement. Large crepitant flexor tendon nodules were present. The erythrocyte sedimentation rate was 43 mm./hr and the serum albumin and globulin concentrations were 3·8 and 4·4 g. per cent. At follow-up the following year she had experienced an excellent recovery. There was some residual swelling, deformity, and weakness of the fingers and toes, and the erythrocyte sedimentation rate had fallen to 11 mm./hr. Three estimations of her S.C.A.T. were all negative (<4).

Only one patient in the group was considered to have made a complete recovery.

Case 6, a man aged 47, had arthritis characterized by an episodic course with complete remissions. Many of the episodes had followed upper respiratory infections and he gave a history of previous rheumatic fever. His first admission to hospital was for a more prolonged arthritis which lasted about a year and started 3 weeks after a sore throat, severe enough to cause dysphagia and cervical lymphadenitis. Small transient nodules were noted on the elbows and he showed a peripheral symmetrical arthritis, mainly affecting the wrists, metacarpophalangeal joints, knees, and feet. Three further attacks of polyarthritis with recovery occurred in the next 4 years.

The distribution of arthritis was considered typical of rheumatoid arthritis and there was never cardiac involvement; nevertheless, the diagnosis of recurrent rheumatic fever would have been equally appropriate.

Some 30 per cent. of patients with rheumatic fever do not develop carditis (and adults are said to be less prone to this complication than children). One further patient in this group is of interest:

Case 7, a woman aged 55, developed in addition to her polyarthritis a myopathy with dysphagia, weakness of voice and limbs, difficulty in coughing, regurgitation of food, and creatinuria of 250 mg./24 hrs. A muscle biopsy showed only thinning of the fibres and no vascular lesions. With corticotrophin or prednisolone her symptoms from both arthritis and myopathy improved, her creatinuria disappeared, and the erythrocyte sedimentation rate fell from 65 to 5 mm./hr. 9 years after the start of the illness her arthritis was quiescent but she still experienced marked weakness if an attempt were made to withdraw steroids. The erythrocyte sedimentation rate remained elevated at 47 mm./hr, and radiographs showed progression of the erosive changes in articular bone. Significant flexor tendon nodules, which had been noted when she was first seen, were still present. Four estimations of the S.C.A.T. had all been negative.

Sero-Negative Group with Atypical Distribution of Arthritis.—Nine patients had an atypical distribution of arthritis, no nodules of any sort, and a persistently negative S.C.A.T. Thus they were both clinically and serologically atypical of rheumatoid arthritis, although no other diagnosis could be made on commonly accepted criteria. They will be described in more detail. They were not an homogeneous group.

Case 8, a woman aged 43, had become pale and ill when aged 38. The next year there was swelling and pain in the proximal and distal interphalangeal joints of the third right finger, and 3 months later she took to her bed. She lost weight and arthritis spread to all limb joints and the spine. A course of gold injections was given but was stopped because of albuminuria. She was admitted to hospital in January, 1954, with severe active polyarthritis, and much inflammation and pain in all joints, but mainly in the larger joints and hips. The erythrocyte sedimentation rate rose to 99 mm./hr and the haemoglobin fell to 76 per cent. A further attempt to give gold therapy led to dermatitis and she was discharged only moderately improved, to be re-admitted in February, 1957. During the interval she had been followed in the out-patient department. Her arthritis had remained active and the erythrocyte sedimentation rate had risen to over 100 mm./hr. For most of the time she had been mainly bedfast. A curious symptom was that of a "burning" sensation which she had experienced in both large and small joints, without other evidence of peripheral neuropathy. It was particularly troublesome at night, and she had to leave her limbs uncovered by the bedclothes in order to obtain relief. This symptom stopped when prednisolone therapy was started. Her lymph nodes were enlarged and there was clinical involvement of all joints, especially marked in the hips. The haemoglobin was normal at 102 per cent. despite her chronic illness. Numerous other investigations were normal or non-contributory. Radiographs showed considerable progression of the hip lesion since 1954, with narrowing of the joint spaces from cartilage destruction and proliferation of bone at the joint margins. There were no erosions of articular bone. Similarly, in the wrists, ankles, and knees, there was osteoporosis with cartilage but not bone destruction and there was bony proliferation at the joint margins. Apart from porosis the radiographs of the fingers and toes were normal.

She failed to do well until routine treatment was supplemented by prednisolone 20 mg./day, after which she was able to get up and resume limited housework. at the follow-up examination in 1957, she had some residual flexion contractures of the hips and the erythrocyte sedimentation rate was 60 mm./hr. The haemoglobin was 98 per cent. Five estimations of the S.C.A.T. had all been negative.

Comment.—The unusual features this patient presented were mainly the large-joint distribution of the arthritis, the absence of articular bone erosion, the primary bone proliferation around the joints, the severe and prolonged constitutional illness without anaemia, and the persistently negative S.C.A.T.

Case 9, a woman aged 53, had noted the sudden onset of acute pain and swelling in the right big toe in 1950. The part was bluish red and the pain was described as "burning". Later the left toe was similarly affected and the following year she suddenly developed inflammation in both wrists. The right knee swelled insidiously and developed a flexion contracture. On each of three admissions to another hospital her illness was diagnosed

as gout, but the serum uric acid was never raised and colchicine did not help her. At age 56 she developed a tense effusion in the right knee, swelling of the bursae under the Achilles tendon insertions, minor pain in the bases of the lateral toes, the left ankle, and both wrists, and some swelling and pain in the second right proximal interphalangeal joint. The conditions responded to rest followed by slow rehabilitation. The erythrocyte sedimentation rate fell from 55 mm./hr to normal levels and joint function became almost normal. The left ankle became painful again but responded to local injections and hydrocortisone, and she was able to do all her housework and to travel several miles each day in order to look after her invalid mother. There was no family history of gout, arthritis, or psoriasis, and nothing to suggest the non-articular features of Reiter's syndrome. Four estimations of the serum uric acid were 3·6 mg. per cent. or less and the S.C.A.T. was negative on four occasions.

Comment.—The atypical features of this patient's illness were the initial gout-like episodes of joint involvement. the subsequent distribution involving mainly the large joints, and the excellent recovery. Her disease fits in with a pattern of involvement and evolution which we have observed in association with some cases of psoriasis, of which, however, there was no other evidence.

The following two cases showed marked constitutional disease associated with a severe central polyarthritis which progressed to complete recovery.

Case 10, an unmarried children's nurse aged 58, was well until she began to lose weight, 28 lb. (12·7 kg.), and felt unwell and easily fatigued. The following year she noted increasing morning stiffness in both legs and there was aching pain referred to the region of the vagina. Stiffness and weakness increased until finally she was unable to get up from a chair unaided. She became ill and feverish, and took to her bed. She was admitted to another hospital where little could be found wrong, except that she was anaemic (haemoglobin 76 per cent., falling to 58 per cent.), had a mild fever (to 100° F. daily) and a high erythrocyte sedimentation rate (38 rising to 65 mm./hr). A retained root of a tooth was removed. 4 days later the left knee swelled for the first time. Her general condition continued to worsen, and there was more pain and stiffness in the shoulders, back and legs. Subsequently she was found to have urine chronically infected with *E. coli* which did not respond to appropriate antibiotics. The right knee swelled painfully and she was transferred to the Manchester Royal Infirmary for further care. Her brother had died at the age of 50 after being crippled for many years with spinal trouble, the nature of which was not known.

On examination, she was thin and pale and ill. Movements of the shoulders and the small joints of the shoulder girdle were limited and painful. The sternomanubrial joint was tender, the chest expansion restricted, the movements of neck and spine painful and reduced to about half normal range, the sacro-iliac joints painful on compression and distraction, the hips painful and restricted, and both knees hot, tender, swollen, and limited. There was much wasting of the thigh muscles.

The remaining joints were normal and systems were normal. The haemoglobin was 62 per cent. with a low mean corpuscular haemoglobin concentration of 28 per cent. The erythrocyte sedimentation rate was 97 mm./hr. The urine was found to be infected with coliform organisms and several excretion and retrograde pyelograms showed three functioning kidneys, two on the left and one on the right. There was an opacity in the right renal substance, presumably a stone; the urine from two of the kidneys was infected, and various antibiotics did not clear the infection. Whilst she was in hospital both wrists and both the second proximal interphalangeal joints of both hands became tender and swollen, but settled again in a few weeks. She was later transferred to the Devonshire Royal Hospital where she was observed for 3 months. Her wasted, ill state continued and did not respond to prolonged (2 months) rest in bed. Pain in the shoulders, sternum, spine, hips, and knees continued to dominate the clinical picture. It was decided to mobilize her, and after she began to get up she started to recover.

At follow-up one year later, at the age of 61, she had fully recovered. No trace of the previous severe illness remained apart from a little creaking in the knees. She was symptom-free and back at work. Thirteen estimations of the S.C.A.T. in 2 years had all been negative.

Case 11, a married woman aged 54, who had suffered from stones in the right kidney for several years, noted the sudden onset of thermal paraesthesiae in the hands, which recovered but were followed in 3 days by pain in the right upper arm which persisted, and then the right shoulder became stiff. At age 56 the shoulder became worse and there was pain in the thighs and neck and stiffness of the spine. At age 57 a right non-functioning kidney was removed for a further stone. The left kidney was normal. The rest of the previous medical history and family history was non-contributory.

Later that year her general health was good. On examination, the peripheral limb joints were normal. The right shoulder allowed only a few degrees of painful movement. The left shoulder moved with pain through half its normal range. Both hips hurt and were limited in abduction and flexion. Pressure on the iliac crests produced pain in the region of the symphysis pubis. Straight leg raising was slightly limited and all movements of the neck and spine were much restricted and painful. The sedimentation rate was 30 mm./hr, and the blood pressure 190/110 mm. Hg. Radiographs were normal. She was investigated in hospital but no further clues as to the aetiology of the disease came to light. She was treated with phenylbutazone 400 mg./day with signal relief of symptoms and was able to resume work, but the treatment caused indigestion and was reduced and

then stopped. She remained well, but 2 years later, at age 58, developed extensive erythema nodosum of both legs. A chest radiograph at the time was normal. The episode was associated with some backache but no recurrence of her arthritis. At follow-up at age 62, she was completely well apart from slight symptomless hypertension. The erythrocyte sedimentation rate, however, was still slightly elevated at 24 mm./hr. Other investigations showed no abnormality. Three estimations of the S.C.A.T. in 6 years had all been normal.

Comment.—Both these patients were female, middle-aged, and had a severe central polyarthritis with constitutional illness and raised erythrocyte sedimentation rate, from which they recovered. The severity of the disease and its excellent recovery, the central rather than peripheral arthritis, the negative S.C.A.T., the absence of nodules, and possibly also the poor symptomatic response to rest in bed, all distinguish their illnesses from typical rheumatoid arthritis. There was never any clinical or radiological evidence of ankylosing spondylitis and the erythema nodosum shown by the second patient was probably coincidental, since the arthritis associated with that condition commonly occurs concurrently and is often limited to one or two of the larger limb joints, particularly the knees. Many of the features of "periarthritis rhizomelique" (Forestier and Certonciny, 1953, 1958) are reminiscent of those shown by these two patients.

Case 12, a married shopkeeper aged 49, noted swelling of the right knee, which was followed by complete recovery after several months. At age 52 he had pain in the sternal region and took 4 weeks off work. The next year he had pain in the left knee and hip and further pain in the sternum and back. He was increasingly disabled and later that year took to his bed. He was admitted to his local hospital and improved with rest in bed and simple physiotherapy. At age 54 he was seen at the clinic for ankylosing spondylitis and thought to be an atypical case of that disease. He was treated with radiotherapy but made no definite response. At age 56 he had an acute relapse with pain in the back, chest, and shoulders, swelling of the right hand and wrist, and general illness and loss of weight. There was no history of dysuria, urethral discharge, venereal disease, conjunctivitis, or dysentery. When admitted to the Manchester Royal Infirmary, he was ill, depressed, thin, and pale, and had thickening of several metacarpophalangeal joints and proximal interphalangeal joints in the right hand. The right wrist was swollen, painful, and limited. The left hand and wrist, both elbows, and both gleno-humeral joints were normal, but the shoulder movements were limited by painful involvement of the acromio-clavicular and sterno-clavicular joints. The hips were normal, the knees showed a trace of fluid, and the ankles were normal, but there was a painful spur under the left calcaneum. The cervical spine was painful and restricted and there was considerable loss of mobility in the lumbar spine which was tender. The erythrocyte sedimentation rate was elevated (80 mm./hr) and the serum proteins were abnormal (albumin, 3·4 g. per cent.; globulin, 4·0 g. per cent.). Radiographs of the spine showed calcification of interspinous ligaments between the first and third lumbar vertebrae. The sacro-iliac joints were somewhat sclerosed with some scalloped erosions, but the peripheral joints showed osteoporosis only. A further trial of radiotherapy to the affected acromio-clavicular joints (in which one side was "mock-treated" as a control) showed no definite response. His ill state continued with frequent flares of arthritis, for about 6 months, and finally settled after a course of gold injections, with complete resolution of all the clinical findings in the peripheral joints. At follow-up at age 57 he was vastly improved and cheerful and had put on weight. He was still having minor episodes of joint pain and there was subluxation and crepitus in the right first metacarpophalangeal joint. The chest expansion had improved to 3 cm., but the lumbar spine was still severely limited. The bursae under both Achilles tendon insertions were painful and swollen and there were tender calcaneal spurs under both heels. The erythrocyte sedimentation rate was normal at 10 mm./hr. Seven estimations of the S.C.A.T. had all been negative.

Comment.—This man showed some of the features of the arthritis of Reiter's disease, namely remittent course, Achilles tendon bursa and calcaneal spur involvement, spondylitis not typical of ankylosing spondylitis, and residual spinal ligamentous calcification and sacro-iliac changes. However, there were none of the other features usually considered essential for this diagnosis. On the other hand, the excellent recovery after a severe constitutional illness, the absence of nodules, the negative S.C.A.T., and the mainly central rather than peripheral joint involvement are against the diagnosis of rheumatoid arthritis.

Case 13, a retired chauffeur, aged 65, noted aching in the right shoulder and the symptoms later spread to the hips, knees, wrists, and spine. The fingers were spared. When admitted to hospital the following year, he was found to be ill with an elevated erythrocyte sedimentation rate (78 mm./hr) and haemoglobin 74 per cent. He went into a good remission after discharge and was not seen again until age 69 when he showed a little residual limitation in the right shoulder, and had developed mild bilateral Dupuytren's contracture. Previously involved joints all showed extensive juxta-articular bony proliferation and Heberden's nodes were present on the fingers. He gave a history of pyelitis and dysuria at the age of 50, but otherwise his past medical history and his family history was not relevant. Four estimations of his S.C.A.T. were all negative.

Case 14, an electrical engineer aged 47, noticed pain and stiffness in the neck, and 3 years later developed localized pain on the medial side of the left knee. The left knee swelled and later the small joints of the hands, wrists, elbows, ankles, and left shoulder became painful. A course of gold injections was followed by an almost complete remission lasting 8 months, when he relapsed, and a second course had no effect. However, he later went into a spontaneous remission lasting 3 years until he developed pain in the left knee and ankle. At age 60 both feet and ankles swelled each evening. He lost weight and became rather breathless but had no cough. At age 62 he was admitted to hospital, where he showed generalized enlargement of lymph nodes, and slight swelling of the metacarpophalangeal joints, wrists, and elbows. The gleno-humeral joints were normal but the acromio-clavicular joints were tensely swollen. The cervical spine and both hips were painful. Both knees were hot, tender, and swollen, and the right knee showed an effusion and flexion deformity. The erythrocyte sedimentation rate was 47 mm./hr. The Wassermann reaction was negative. Radiographs showed massive "fluffy" bone proliferation around the knees and for a short distance along the femora and tibia. Similar but more marked changes were present in the ankles (Fig. 1) and extended well beyond the limits of the synovial membrane. These changes suggested sub-periosteal new bone growth. There was minor bone proliferation around the hips and sacro-iliac joints consistent with osteo-arthritis. He was sent home to rest in bed and made a good functional recovery, but 3 years later there was still thickening and limitation of the wrists, elbows, and knees with flexion contractures. The hips were normal and there was considerable restriction of spinal movements. The erythrocyte sedimentation rate was again 47 mm./hr. At age 67, at the follow-up examination, both knees were still painful and hot but the left was almost ankylosed, whilst the right knee showed a limited range of movement. There was bony thickening in the knees, ankles, and elbows, but the hands were normal apart from a few Heberden's nodes, and the shoulders showed an almost full range of painless movement. The erythrocyte sedimentation rate was elevated at 31 mm./hr. Six estimations of the S.C.A.T. had all been negative.

Fig. 1.—Case 14, sero-negative with atypical distribution of arthritis. Radiograph of ankle showing changes suggesting sub-periosteal bone growth.

Comment.—Both these patients developed an inflammatory polyarthritis with constitutional illness followed by bony proliferation around the joints; in one this proliferation was marked and suggested a periosteal reaction rather than exuberant osteophytic formation. The degree of constitutional illness and the persistently elevated erythrocyte sedimentation rate in these cases, as well as the development of flexion contractures, make it unlikely that they fit in with the picture of generalized osteo-arthritis (Kellgren and Moore, 1952). They would in common usage be described as cases of "mixed arthritis", *i.e.* with a mixture of rheumatoid and osteo-arthritic changes. Mason, Murray, Oates, and Young (1959) have commented on exuberant periosteal new bone formation near joints and feel that "florid, fluffy new bone does appear to be a feature of Reiter's disease and of ankylosing spondylitis"; but of these diagnoses there was no further evidence in these two patients.

Case 15, a female slipper worker, had developed a swollen right knee at age 12. This was treated as tuberculous at another hospital, but subsequently the left knee swelled and a synovial biopsy did not confirm this disease. Between the ages of 15 and 23 years she could get about normally, but at age 23 the knees deteriorated and from that time the right wrist and left elbow and fourth metacarpophalangeal joint swelled and hurt and she noted pain in both hips and in the left temporo-mandibular joint. She was admitted to the Manchester Royal Infirmary at age 28, and a further synovial biopsy showed a picture suggestive of rheumatoid arthritis. The erythrocyte sedimentation rate was raised to between 17 and 45 mm./hr, but all other investigations, including cultures of the synovial fluid for tuberculosis, were negative. She improved on rest in bed, salicylates, and serial splinting of the knees. When she was seen at follow-up at age 31 her functional state was good and she was able to look after a house and child. There was still swelling, tenderness, and restriction of the right wrist, left elbow, both hips, and both knees, but the spine was very mobile and the hands and feet were free of disease. The erythrocyte sedimentation rate was still elevated at 34 mm./hr. Six estimations of the S.C.A.T. over 5 years had all been negative.

Comment.—Monarticular arthritis resembling (and often treated as) tuberculosis is a not uncommon way in which juvenile rheumatoid arthritis

may present itself. The S.C.A.T. is commonly negative in Still's disease (55 per cent. of 142 cases each tested an average of 9·5 times, were consistently found to be negative by Bywaters, Carter, and Scott, 1959). However, it is questionable whether all cases of juvenile polyarthritis not otherwise diagnosed should be equated with rheumatoid arthritis as it occurs in adults.

Case 16, a farmer aged 47, developed acute pain and swelling in the left thumb and wrist after forking hay, and subsequently noted pains in the left knee, left hip, and left elbow. At age 54, he began to feel lumbar pain and stiffness, worse after heavy lifting, radiating to the lower abdomen and groins. The still swollen left wrist was explored at his local hospital but no infection was found. Subsequently there was increasing pain in the left elbow, left shoulder, and back despite excellent general health. He was admitted to hospital for increasing disability. Abnormalities were limited to the connective tissue and joints. There were large, well-defined, rubbery, cushion-like thickenings of the dermis over the hands corresponding to pressure areas where he held his farm implements. Similar large (1 × 2 cm.) dermal cushions had developed around the ankles and on the dorsum of the feet corresponding to sites of pressure of his boots. The left wrist was swollen and showed only 5° of painful movement. There was slight general restriction of movement in the left hip. The spine was generally tender and was flattened in the lumbar region. Other joints had normal or only slightly restricted movement without swelling, although many of them were painful. The erythrocyte sedimentation rate on three occasions was 14, 19, 25 mm./hr. Radiographs revealed extensive cartilage destruction and bone erosions in the left wrist and numerous Schmorl's nodes in the spine. All the investigations were normal.

The patient was treated with analgesics and a spinal support and resumed his farming, but his condition deteriorated and 2 years later at follow-up he was found to be much more crippled. There was swelling and painful limitation of both knees, both elbows, and the left ankle. The shoulders were painful and on occasions he had been unable to raise his arms. His neck was stiff and he had pain in the hips on walking. There had also been some occasional swelling in the proximal interphalangeal joints of the right hand. The erythrocyte sedimentation rate was 37 mm./hr. Four estimations of the S.C.A.T. in 2 years were all negative.

Comment.—This man's polyarthritis was chiefly seen in the larger limb joints. Rheumatoid arthritis cannot be excluded, but the relative sparing of the small joints of the hands and feet is atypical. On the other hand there is some evidence that he may have had an underlying dystrophy which did not permit his bones, joints, and fibrous tissues to stand up to hard work in the normal way, resulting in the development of numerous Schmorl's nodes in the spine and painful arthritis of the wrist, knees, and elbows, and localized hypertrophy of the dermis over sites of intermittent pressure. These lumps were not rheumatoid nodules, nor were they the nodules of cutis elastica or pseudoxanthoma elasticum.

Other Diseases

Eleven patients had confirmed or probable disease other than rheumatoid arthritis at follow-up: psoriatic arthropathy (4), gout (1), reticulohistiocytosis (2), Takayushu's syndrome (1), Reiter's disease (1), generalized osteo-arthritis (1), myelomatosis (1).

Psoriatic Arthropathy

Case 17, a baker aged 41, had developed painful feet in his early 30s, which had continued until a generalized polyarthritis developed. This was thought to be indistinguishable from rheumatoid arthritis, and he was treated with cortisone during a large-scale therapeutic trial of that hormone. There was little immediate improvement, but it was not possible to wean him from this treatment without provoking a relapse. After 6 months he returned home and gradually improved sufficiently to resume his business, but was still taking 100 mg. cortisone daily, and continued in this way with variable but continuous joint symptoms. At age 46, about 15 years after the first onset of joint symptoms, he developed a patch of psoriasis on one leg. The following year the psoriasis became generalized and he complained of weakness of the limbs. He was admitted to hospital where, in addition to his psoriasis, he showed painful limitation of movement in the wrists, ankles, and tarsal joints, with some swelling and instability in the metacarpophalangeal joints and a localized, hot, tender active arthritis of the left midtarsal region. There were no nodules of any sort. The erythrocyte sedimentation rate was 17 mm./hr. A radiograph of the joints showed only slight osteoporosis with minimal evidence of bone erosion. Nine estimations of the S.C.A.T. over 6 years had all been negative.

Case 18, an engineer and ex-athlete aged 53, had had a meniscus removed from the left knee at age 33 following a football injury. The next year the right knee swelled and later developed a flexion contracture. At age 34, he noted painful swelling of both big toes, which persisted. At age 43, the terminal interphalangeal joints of the right thumb and index fingers swelled and there was pain in other joints associated with constitutional illness and a 2-stone weight loss. When he was admitted to hospital the following year, polyarthritis had involved a number of small joints in the hands and the involvement of the right knee was curiously localized to the outer aspect, where there was redness, swelling, and focal tenderness. The left knee was less involved and there

was dorsal subluxation of the lateral toes. The erythrocyte sedimentation rate was 32 mm./hr. He was treated with gold injections, but both wrists and the right sterno-clavicular joint swelled and the erythrocyte sedimentation rate rose to 70 mm./hr. At follow-up, he was still troubled by morning stiffness and painful knee contractures, but his general health was good. His hands presented a remarkable appearance, which was regarded as characteristic of psoriatic arthropathy, although he had at no time shown psoriasis of the skin. The terminal phalanges of the right thumb and index finger were grossly swollen and shortened, with deformity and patchy discoloration of the nails. The terminal interphalangeal joints of these fingers were destroyed and "flail". Similar but less advanced changes were present in the terminal joints of the right and left middle fingers, that on the left being associated with "beef sausage" appearance, *i.e.* uniform pink, brawny, soft tissue swelling of the whole finger, involving both joints and tendon sheaths, and easily distinguished from the moist pale lilac skin and fusiform swellings of typical rheumatoid arthritis. Both wrists showed a fibrous ankylosis, but the elbows, shoulders, neck, spine, and hips were clinically normal. Both sterno-clavicular joints and the left knee were tender and swollen but there was a relatively painless fibrous ankylosis of the right knee and the tarsal joints and lateral toes. Both great toes showed uniform brawny swelling and limitation of movement, with brown pigmentation of overlying skin and discoloration of the nail. There were no nodules. The erythrocyte sedimentation rate was 76 mm./hr. Radiographs of the hands (Fig. 2) and toes confirmed the soft-tissue swelling and gross terminal joint destruction as well as erosions in other small joints. Eight estimations of the S.C.A.T. had all been negative.

Case 19, a woman aged 64, had first experienced polyarthritis 8 years previously; it had started suddenly in the right thumb and spread to all the fingers and toes. She was feverish despite the administration of penicillin and had lost weight. When she was seen as an outpatient, there was tender swelling of all the finger joints, massive thickening of the finger flexor tendons, and pain in all large joints. Her disease went into a remission for 5 years after a course of gold therapy, but at age 62 she again noted pain in the neck, shoulders, hands, knees and jaw, for which she received prednisolone with some benefit. When she was seen at follow-up 2 years later there was no evidence of psoriasis except for some pitting of one thumb-nail, but the arthritis was very suggestive of psoriatic arthropathy. The hands were pink, warm, and dry, and all the terminal interphalangeal joints were swollen as were some of the proximal interphalangeals, so that several fingers had the typical "beef sausage"

Fig. 2.—Case 18, psoriatic arthropathy. Radiograph of hands showing soft-tissue swelling, gross terminal joint destruction, and erosions in other small joints.

appearance. However, the hands were relatively painless and still useful. There was focal pain on the medial aspect of the right knee. Both heels were tender and had in the past been a major cause of disability. There were arthritic changes in the small joints of the feet. Radiographs of the hands confirmed the extensive destructive changes in the terminal and proximal interphalangeal joints. The results of five estimations of the S.C.A.T. in 7 years had all been negative.

Case 20, a man aged 20, had had a long stay in a children's hospital for polyarthritis at age 9. The condition had healed completely but at age 16 the left foot had swelled. He was seen as an out-patient and found to have slight swelling of the interphalangeal joints of the fingers in addition to a warm, tender left tarsus and big toe, and a localized area of warmth, tenderness, and swelling near the left lateral tibial condyle with limitation of knee flexion. The chest expansion and spinal movements were slightly limited and the erythrocyte sedimentation rate was 37 mm./hr. Later in the same year he was admitted to hospital because of a relapse with fever and acute polyarthritis. He was treated with rest in bed, aspirin, and suitable plasters, but 5 months later developed a large effusion in the right knee and the right tarsus became painful. He was also noted to have a right Achilles tendinitis. From these troubles he made an excellent recovery. When seen at follow-up at the age of 20 he was well, at work, and indulging in strenuous sports. However, the right knee was still swollen and contained an effusion, the chest expansion was 3 cm., and all spinal movements were restricted. Radiographs of the hands, knees, and feet were normal but there was almost complete obliteration of both sacro-iliac joints (Fig. 3), the changes being more pronounced on the right. He gave a previous history of acute psoriasis at age 7, which had been diagnosed and treated in a hospital for skin diseases, but which had cleared up entirely before his polyarthritis had begun. The results of five estimations of the S.C.A.T. had all been negative.

Comment.—No definition of psoriatic arthropathy has been universally accepted. There is fairly general agreement that the inflammatory arthritis confined to the terminal interphalangeal joints, associated with nail changes on the corresponding fingers, deserves to be considered as an entity separate from typical rheumatoid arthritis. Such changes, however, may also occur as part of a general polyarthritis, with or (as in Case 18) without psoriasis of the skin. Most authors who have studied the S.C.A.T. or related agglutination reactions have noted that these tests are usually negative in, and rheumatoid subcutaneous nodules usually absent from, patients who show psoriasis with any

Fig. 3.—Case 20, psoriatic arthropathy. Radiograph of pelvis, showing almost complete obliteration of sacro-iliac joints, more pronounced on the right.

form of arthritis (Kellgren and Ball, 1959; Ziff, 1957; Wright, 1957, 1959; Jacqueline, Podliachouk, and Eyquem, 1956; and many others). These negative associations are so frequent as to make it likely that most cases of arthritis associated with psoriasis represent a disease or diseases distinct from rheumatoid arthritis. Other clinical features sometimes (but not invariably) present to help differentiate the arthritis of this condition include:

(1) Acute, often gout-like onset;
(2) Focal areas of tenderness and inflammation around large joints;
(3) Severe destruction in some joints with complete sparing of others;
(4) A mainly large-joint distribution;
(5) Where the fingers are involved, cylindrical brawny swelling with pink, warm, and often dry overlying skin—the "sausage finger" of Weissenbach (1938).
(6) A tendency for destructive arthritis of the terminal interphalangeal joints often associated with discoloration and subungual hyperkeratosis of the corresponding nail;
(7) Radiological appearances of bone proliferation as well as destruction around involved joints.

The degree of psoriasis bears no relationship to the amount of arthritis with which it may be associated, and varies from generalized exfoliation to small inactive patches of rash, often hidden in the navel or around the anus, and easily missed. Moreover, the rash may clear up entirely in cases showing persistent arthritis, only to reappear from time to time. Many patients give a history of noticing arthritis before the psoriasis (as in Wright's series), and Wright (1957) has written: "It is tempting to suggest that some cases of erosive arthropathy with a negative differential agglutination test are destined to develop psoriasis", a sequence which was observed in Case 17 after 15 years of arthritis. Sharp (1957) has called attention to the association of psoriasis and atypical spondylitis seen in the fourth of these cases.

GOUT.—This was seen in one male patient.

Case 21, a robust police inspector aged 48, developed pain in both feet, of gradual onset, later spreading to all major joints, as well as the fingers, jaw, and neck. There was no family history of arthritis. When he was first seen at age 46, his hands were pink and cool, and there was slight limitation of movement in all finger joints, as well as of the shoulders, hips, and neck. The haemoglobin and white cell count were normal, but the erythrocyte sedimentation rate was 33 mm./hr. A diagnosis of rheumatoid arthritis was made. At follow-up, at age 48, there was improvement in the joints but small nodules had appeared on both elbows. The haemoglobin and white cell count were still normal, the erythrocyte sedimentation rate was 19 mm./hr, and two estimations of the serum uric acid were 5·2 and 6·8 mg. per cent. respectively. Radiographs showed ill-defined cystic changes in the bone ends, which were picked by an independent observer unaware of the clinical findings, as more suggestive of gout. Further investigation had not been permitted. The results of five estimations of the S.C.A.T. were all 4 or less.

Comment.—The evidence for gout lacks proof, but nevertheless, Ludwig, Bennett, and Bauer (1938) noted gout presenting in such a manner, and this diagnosis seems at least as tenable as that of rheumatoid arthritis. In no other case in this follow-up series was the serum uric acid level raised, and the two observations recorded here are unlikely to be due to experimental error.

RETICULOHISTIOCYTOSIS.—Two patients were thought to have reticulohistiocytosis (Warin, Evans, Hewitt, Taylor, Price, and Middlemiss, 1957) and in one, biopsy proof was obtained.

Case 22, a married woman aged 39, was well until age 33 when she experienced prurigo of the hands, without visible rash, lasting 3 months; 9 months later her fingers became cold, white, and painful, and small nodules and tiny translucent papules developed on the backs of the fingers and around the nails. The fingers became stiff and so painful that, at age 34, she was referred for surgical treatment of the Raynaud's phenomenon, but this was not done because the condition improved spontaneously. She was admitted to the Manchester Royal Infirmary, at age 35, for pain and stiffness in wrists, elbows, shoulders, feet, and knees associated with weight loss, generalized lymphadenopathy, and nodules, not only in the dermis of the fingers but also attached to the finger flexor tendons and around the wrists and ankles. There were objective signs of arthritis of the elbows, wrists, and knees, and all other joints except the spine were painful. The erythrocyte sedimentation rate was only slightly raised, and the blood count, serum proteins, and urine were normal. She was initially considered to have a rheumatoid arthritis in which connective tissue changes were severe whilst inflammatory reactions were slight. A course of gold injections was started and the patient returned home, since when she has managed with gradually increasing difficulty. Her son, aged 12, was normal, but her mother, who was at that time normal, later developed a polyarthritis of hands, wrists, and feet, and her aunt, too, had had some form of rheumatism.

At follow-up examination the patient was of normal build and colour. Her disabilities arose mainly from an enormous number of small nodules. In the hands these were 1 to 5 mm. in size, rounded, raised, painless, firm, brown or violet, intracutaneous granulomata, and occurred in the pulps as well as on the backs of the fingers. A particular feature was the presence of a

Fig. 4.—Case 22, reticulohistiocytosis. Nodules on fingers.

corona of tiny granulomata in the edge of the nail fold at the base of each nail (Fig. 4). Other nodules affected the tendons, which were massively enlarged both in the palms and on the extensor surfaces. Limitation of finger movement was probably due to impaction of these tendon nodules in their sheaths. There were similar nodules in the Achilles tendons and around the ankles. In the forearms and feet the tendon nodules produced a "beaded" appearance. There was no generalized rash, and despite a careful search only three small lesions involving the skin were found elsewhere than on the fingers. One, 2 mm. in diameter, was present over one knee and there were two over the left elbow; the latter were removed for histological examination. There were no xanthelasma and no mucous membrane changes. Small effusions were demonstrable in both knees and there was dorsal subluxation of the lateral toes as seen in rheumatoid arthritis. The wrists contained small effusions and there was some swelling of both second and third metacarpophalangeal joints with lesser swelling of other knuckle and finger joints. The general physical condition was otherwise normal. The haemoglobin was 80 per cent., total white cell count 7,100 cells per c.mm., differential cell count normal, serum uric acid 3·5 mg. per cent., and erythrocyte sedimentation rate 32 mm./hr. The biopsy was reported (by Dr. J. Ball) as follows:

"Reticulohistiocytoma. The middle and lower dermis is occupied by a nodule (approximately 1 mm. in diameter) consisting of cells with one, two, or several nuclei. The nuclei are pale, the cytoplasm abundant and without conspicuous granules. The multi-nucleate cells give a weak reaction for lipid with Sudan black, which disappears after extraction with hot methanol and chloroform. Mild acid hydrolysis does not increase the uptake of Sudan-type dyes. There is some periodic-acid-Schiff-positive material in the cells, not removed by fat extraction. None of these reactions is strong, but they suggest that the cytoplasm may contain both lipid and neutral polysaccharide."

Radiographs of the knees (Fig. 5), hands (Fig. 6), left foot (Fig. 7B), and pelvis were taken, and radiographs of the hand and feet which had been taken during her previous stay in hospital were available for comparison. These showed gross cystic defects of bone in the sub-

Fig. 5.—Case 22, reticulohistiocytosis. Radiographs of knees.

6 (A)

6 (B)

Fig. 6.—Case 22, reticulohistiocytosis. Radiograph of left hand when first seen (A) and 4 years later (B). Flexor deformities of fingers result from tendon nodules. Deposits near joints mimic rheumatoid arthritis.

7 (A)

7 (B)

Fig. 7.—Case 22, reticulohistiocytosis. Radiograph of left foot (B). The corresponding foot of Case 23 (the patient's mother—not one of our follow-up series) shows typical rheumatoid arthritis (A).

chondral regions. The "cystic" appearances had the largest diameter in the knees. In the hands the "cysts" were smaller and appeared to have broken through into the joint space itself. The articular cartilage, where not involved by a "cyst", retained its normal thickness and the bones were not particularly porotic.

Case 23, the mother of Case 21, was not seeking medical advice, but was seen to have hand and wrist changes which appeared to be due to typical rheumatoid arthritis. Full examination was not permitted, but reticulohistiocytic skin lesions were not present on the hands, feet, and face. There was an early Dupuytren's palmar fascial thickening opposite the right and left third and fourth fingers, without contracture, and both wrists were tender, swollen, and limited. The second and third metacarpophalangeal joints were also swollen and flexed. There were small but significant flexor tendon nodules, rheumatoid deformities of the toes, and a discharging sinus over a left hallus valgus. Radiographs of her hands and feet were taken, the latter (Fig. 7A) being practically identical with those shown by her daughter. No blood test was obtained for S.C.A.T., but the possibility that the mother also had this disease could not be excluded. If she did not have reticulohistiocytosis, the radiographs illustrated the great resemblance between this disease and rheumatoid arthritis.

Comment.—The comparative absence of skin lesions in Case 21 was intriguing. It was tempting to suppose that patients might exist who would show the condition without any skin lesions, and accordingly the patients in this study were reviewed with this in mind. One patient showed large tendon nodules and her radiographs showed cystic defects of bone with relative preservation of bone density.

Case 24, a woman aged 51, developed painful knees at age 41. At age 47 she developed generalized polyarthritis and the following year was found to have thickening of the flexor tendons in the hands, swelling of the small joints of hands and feet, and large effusions in the knees. She was thought to have typical rheumatoid arthritis and was treated with gold injections. She again improved until age 56, when there was a slight recurrence of stiffness. She was deaf and gave a family history of otosclerosis. At the follow-up examination the striking finding was that of large, visible, crepitant nodules in the flexor tendons of the hands. The finger joints were limited in range and a little tender, and all other joints showed slight painless limitation of movement. There were no skin nodules or rash. The haemoglobin was 90 per cent., white cell count normal, and serum uric acid 3·5 mg. per cent. A radiograph of the hands (Fig. 8, opposite) was reported (by Dr. G. B. Locke) as showing "very pronounced cystic changes in the lower end of each radius, carpal bones, the base of the thumb metacarpals and subarticular region of the metacarpophalangeal joints". The S.C.A.T. was tested over a period of 5 years and was negative on each occasion.

Takayushu's Syndrome

Case 25, a woman aged 50, had had chorea at age 17. At age 30 her left elbow swelled and was painful for many months. At age 33 she became pregnant and with the pregnancy became ill. The foetus died at 3 months but was not delivered until the 6th month. Subsequently the patient developed severe Raynaud's phenomenon, with recurrent attacks of colic, diarrhoea, and vomiting. A laparotomy was performed for one of these attacks, signs of a peritonitis were found, and the patient was nursed in a sitting position. During this time both knees became stiff and painful and the pains later spread to the wrists, elbows, shoulders, and back. At age 46 her health deteriorated, she noted flitting areas of skin soreness, many reddish nodules, and bruising. At age 48 there was sudden, severe, lower abdominal pain spreading to the back, and a week later sudden pain in the left calf, with claudication and pain on walking. There were episodes of patchy swelling and pain about the head and face, and she was breathless on exertion. She was admitted to hospital because of increasing pain from her knees and because of the claudication.

The pulses were absent in the left leg and variable in the right arm. The peripheral arteries, including the carotids, were thickened, and the carotid sinus was sensitive to very slight pressure. There were clinical and radiological signs of a slight mitral stenosis. The presence of oesophageal varices, disturbed liver function tests, facial pigmentation, and telangiectases suggested hepatic cirrhosis. Shortly after her admission to hospital the right foot became pulseless. She was given anticoagulants and corticosteroids with relief of pain, but developed further evidence of arterial occlusion in the coronary and possibly renal arteries. She died from left ventricular failure. *Post mortem* examination was not permitted.

The joint findings are best described as a "subluxing arthropathy", *i.e.* there was gross dislocation of the toes at the metatarsophalangeal joints, and of the carpus at the wrist joints, with only minimal changes in subchondral bone, despite a generalized osteoporosis. The "erosions" or defects seen could probably be regarded as secondary to the subluxation, rather than as evidence of an erosive synovitis (Fig. 9, opposite).

The erythrocyte sedimentation rate was 80 mm./hr, and the white cell count normal. Repeated search for L.E. cells was unsuccessful. The S.C.A.T. was negative on nine occasions over a period of 8 months just before the patient's death.

Comment.—This patient showed evidence of a generalized arteritis with progressive occlusion. The long history of illness, the sensitive carotid arteries, the thickened arteries generally, the scattered nodular rash, the raised sedimentation rate, suggested "young female arteritis" of Takayushu's disease (Takayushu, 1908). Nine out of 28 such patients reviewed by Ask-Upmark (1954) had some evidence of generalized rheumatism, and a similar proportion in his second review (Ask-Upmark and

8 (A) 8 (B)

Fig. 8.—Case 24, possible reticulohistiocytosis. Radiograph of left hand when first seen (A) and 5 years later (B). Flexion contractures of the fingers result from large tendon nodules. "Cysts" near joints are compatible with rheumatoid arthritis or reticulohistiocytosis.

Fig. 9.—Case 25, Takayushu's syndrome. Radiograph of wrist, showing subluxation.

Fajers, 1956). It is suggested that the arthropathy noted can best be regarded as part of the Takayushu syndrome, since it was neither clinically nor serologically typical of rheumatoid arthritis. Alternative diagnoses, unlikely but not excluded by the evidence available, were polyarteritis nodosa affecting mainly the larger arteries and Jaccoud's syndrome (Bywaters, 1950).

MYELOMATOSIS

Case 26, a housewife aged 45, developed pains in the right hand, right scapula region, and back, worse at night. 8 months later she developed symptoms referable to many joints with swelling in front of the wrists. Movement of the fingers was limited by thickening of the flexor tendons. A biopsy of the tendons showed a featureless granulomatous material. Her condition worsened, and a year after onset she showed swelling of the second and third metacarpophalangeal joints of the right hand and there was pain in many other small joints of the hands. The outer metatarsophalangeal

joints were painful and subluxed and effusions were present in the knees. She was pale and ill but physical examination disclosed no other abnormalities. The erythrocyte sedimentation rate was 42 mm./hr, serum albumin 4·2 g., and globulin 2·2 g. per cent. The haemoglobin fell from 60 to 48 per cent. The white cell count was normal or low on several occasions. The serum uric acid was 5·5 mg. per cent. The urea clearance was subnormal, and the urea showed a fixed specific gravity. Protein was absent from the urine until about 13 months after the onset of disease, when a proteose was found; 3 months later this proteose showed the characteristics of Bence Jones protein. A review of the previous biopsy and other investigations did not disclose any diagnostic evidence of myelomatosis. She was discharged to her home but was re-admitted 18 months after the first onset with anaemia, leucopenia, pain in most joints, contractures of the knees, and a nodule on one elbow. Radiographs taken a few days before her death showed erosions of articular bone in one hip and also changes in the long bones and pelvis "suspicious of myelomatosis". Previous radiographs had all been normal. Five estimations of the S.C.A.T. had all been normal. At autopsy widespread myelomatosis was found.

Comment.—Rheumatoid arthritis could not be excluded on clinical grounds, and was indeed the diagnosis for most of the course of the disease. A polyarthritis, mainly of the small joints, with "rheumatoid" deformity of the toes, effusions into and later contractures of the knees, nodular thickening of the tendons in the hands, and a subcutaneous nodule on the elbow all pointed to this diagnosis. Proteosuria was the first definite sign of myelomatosis, but before this the negative S.C.A.T. had indicated that rheumatoid arthritis was possibly not the correct diagnosis. The granulomatous deposit in the wrist was probably the "para-amyloid" sometimes seen in myelomatosis.

Reiter's Disease and Aortitis

Case 27, a motor driver aged 36, had developed at age 32 a non-gonococcal urethritis followed by stiffness of the back and hips and pains under the right heel and in both shoulders, the neck, right wrist, and right ankle. Moderate disability for 3 years was followed by a relapse with illness, orchitis, back pain, and transient conjunctivitis. He was admitted to hospital and was found to be pale and ill with signs of a free aortic regurgitation. The lower spine was almost rigid and there was active arthritis of the knees, left shoulder, right wrist, right ankle, and first metatarsophalangeal joints, with regional muscle wasting. The erythrocyte sedimentation rate was 84 mm./hr, and haemoglobin 76 per cent. The electrocardiogram showed a prolonged P-R interval (0·4 sec.). Radiographs showed only osteoporosis around the involved joints. A small amount of fluid, of normal appearance but with an increased cellularity, was aspirated from one knee. At age 38 the patient died during an emergency laparotomy for intestinal obstruction, but no *post mortem* examination was made. The clinical diagnosis was "rheumatoid arthritis" with aortic valve disease, presumably rheumatic. Sixteen estimations of the S.C.A.T. had all been negative.

Comment.—This patient showed the syndrome of spondylitis, peripheral joint involvement, and free aortic regurgitation associated with a prolonged P-R interval which has been described by a number of authors since the original publication of Clark and Bauer (1948). These workers regarded the syndrome as a variant of rheumatoid spondylitis, and others (Graham and Smythe, 1958) as a form of ankylosing spondylitis, but I feel, for a variety of reasons, that it is best regarded as a complication of Reiter's syndrome.

Primary Generalized Osteo-Arthritis

Case 28, an unmarried woman aged 61, was admitted to hospital in 1956 with painful joints and stiffness of the neck of one year's duration. She had previously noted episodes of pain and swelling in the knees. Her general health was excellent and she had gained weight. The physical and radiological findings were those of a generalized osteo-arthritis, but the severity of symptoms and high erythrocyte sedimentation rate (83 mm./hr) suggested rheumatoid arthritis. The following year she had lost all disability, but had the deformities of osteo-arthritis, namely Heberden's nodes, adducted thumbs with bony enlargement of the carpometacarpal joints, painless bony enlargement of other finger joints and knees, and limitation of movements in the lower neck. The erythrocyte sedimentation rate had fallen to 47 mm./hr. Four estimations of the S.C.A.T. were all negative, and there was never any evidence of subcutaneous nodules, nor were erosions seen in the bone radiographs.

Comment.—A moderate rise in the erythrocyte sedimentation rate may accompany primary generalized osteo-arthritis (Kellgren and Moore, 1952), but elevation to this degree is exceptional. All other features of this patient's illness pointed to that diagnosis, however, and away from the diagnosis of rheumatoid arthritis.

Discussion

The correlation of a positive S.C.A.T. and the fully-developed picture of rheumatoid arthritis with nodules is practically 100 per cent. (Kellgren and Ball, 1959), an outstanding result for any biological diagnostic test. Compare, for example, the correlation of the antistreptolysin titre and Group-A β-haemolytic streptococcal infection which is 80 per

cent. (Mote and Jones, 1941). The association of severe "rheumatoid-like" chronic polyarthritis and a negative S.C.A.T. is therefore apparently exceptional; such a situation might arise from several causes, related either to the disease or to the test. Population studies (Kellgren and Lawrence, 1956) show a continuous curve for the distribution of titres in the test, the usual dividing line of a limiting dilution of 1 in 32 is arbitrary and is based on the best correlation with clinical findings in a group of patients. A lower titre might be significantly "positive" for an individual patient. Like all serological tests it is subject to one- or even two-tube errors. In this study repeated testing and a titre of 1 : 8 as highest acceptable negative should have minimized these effects. Others have reported on the presence of circulating inhibitors of the S.C.A.T. separable by fractionation of serum. Both the absence of such inhibitors, or their removal to leave a positively reacting residue, have been regarded as diagnostic of rheumatoid arthritis (Ziff, Brown, Lospalluto, Badin, and McEwen, 1956). Sera from all the patients who remained sero-negative in this study have been tested for inhibitors in a similar way, so far fruitlessly, perhaps for technical reasons. Both in juvenile rheumatoid arthritis (Bywaters, Carter, and Scott, 1959) and in surveys of the adult population, especially in the first three decades, the frequency and titre of positive S.C.A.T. tests increases with age. The average age of the patients under study was 52 years, which is beyond the range at which age noticeably influences these results. Nevertheless, the age-effect may explain the low titres in the two patients under 30 years of age at the time of follow-up. Thus, these several technical considerations related to the test cannot explain the persistently negative results seen in the majority of these patients. Considerations related to the disease, on the other hand, do explain some cases, particularly those eleven patients who were found at follow-up to have proved or probable diseases other than rheumatoid arthritis. Hall, Mednis, and Bayles (1958) have noted a similar experience. In our twelve patients who eventually developed a positive S.C.A.T., the majority (ten) also developed a completely typical clinical picture, with symmetrical involvement of peripheral joints, and in most cases, rheumatoid olecranon nodules. It seems likely that the original arthropathy, though sufficiently widespread and active to qualify for this study, was in fact a manifestation of an incomplete development of the total disease of rheumatoid arthritis. We may note the duration and marked severity in Case 2, who developed severe, progressive arthritis, yet 15 years after onset was still sero-negative, despite fibrinoid necrosis of sub-synovial tissue. Sero-conversion was not observed until 23 years after onset, by which time crippling destructive changes had taken place. Parenthetically, it is possible that repeated and non-rheumatoid arthropathy might lead to a generalized rheumatoid arthritis by way of a sensitization reaction, in the same way as accidental or operative trauma to a joint sometimes appears to be followed by the development of generalized rheumatoid arthritis. This kind of sequence seemed possible in Case 3 with a 12-year history of intermittent hydrarthrosis, limited until quite recently to the knees.

The S.C.A.T. may become negative in patients who are doing well (De Forest, Mucci, and Boisvert, 1956) and we have seen several examples of this sequence. The opportunity to continue observations on the S.C.A.T. after a remission of both blood pathology and arthritis is not common; nevertheless, in one other patient who showed the sequence, the S.C.A.T. promptly reverted to positive when the arthritis relapsed after a long interval. Thus it seems unlikely that the patients in this study had been sero-positive at an earlier (unobserved) stage of their disease and were sero-negative but still active on the first presentation. It seems probable, therefore, from this study of thirteen patients who eventually became sero-positive, that some may have typical, active, and severe rheumatoid arthritis for many years, at least 15 in one instance, before sero-conversion occurs. With this evidence it is possible to conclude that the 23 patients who remained sero-negative at follow-up, and who had a typical distribution of arthritis, were examples of an incompletely developed rheumatoid arthritic process. However, it is intellectually unsatisfactory to imagine a *forme fruste* of a disease which is yet severe enough to be rapidly fatal, as in Case 4. Clearly we need to know more about what determines the appearance of the rheumatoid factor in the blood stream in patients with otherwise typical and severe rheumatoid arthritis.

The eight patients with atypical polyarthritis and a persistently negative S.C.A.T. are difficult to accept as having some form of rheumatoid arthritis as we ordinarily know it. They are not an homogenous group and if they do represent atypical forms of known polyarthritic disorders, might in five out of eight cases be better fitted in with disorders such as Reiter's disease or psoriatic arthropathy. Two patients at least (Cases 10 and 11) seem to be examples of an as yet undescribed polyarthritic disease or diseases, unless they are considered to have "periarthritis rhizomelique" (Forestier and Certonciny, 1953, 1958). Recognition of such

cases is important, both from the point of view of prognosis of the individual, and of studies of prognosis generally in rheumatoid arthritis related to the S.C.A.T. Thus several observers have noted that patients with sero-negative "rheumatoid arthritis" have a better prognosis than those who are sero-positive (Duthie, Brown, Knox, and Thompson, 1957; De Forest, Mucci, and Boisvert, 1956; Otten and Westendorp Boerma, 1959). The inclusion of patients with sero-negative polyarthritis other than rheumatoid arthritis in such studies, might have contributed to this favourable impression. Nevertheless, the presence of a persistently negative S.C.A.T. is compatible with severe deformity or even with a fatal outcome in patients with a typical distribution of arthritis.

Similar considerations apply to studies of treatment in rheumatoid arthritis. The inclusion of sero-negative patients, destined to develop polyarthritic disorders other than rheumatoid arthritis, may introduce bias into therapeutic trials if distributed unequally between treatment groups, or at best will "dilute" any differences between treatment groups which may be due to the effects of treatment. Kellgren (1957) has written:

> "In the small series studied in this trial (early rheumatoid arthritis treated with cortisone or aspirin), the prognosis of patients giving only negative results was much better than those giving only positive results, but there appeared to be no difference between those giving only positive results and those giving both positive and negative results in the test [S.C.A.T.]. Among the patients in whom the test was always negative, there were several with severe widespread polyarthritis and a high E.S.R. on entry to the trial, and such negative tests and good prognosis cannot be entirely explained in terms of trivial disease. In therapeutic trials, sheep cell agglutination tests should be performed regularly and patients giving only negative results studied separately."

It would seem wise to apply this principle to all reports of the effects of treatment, prognosis, or associated features of "rheumatoid arthritis", so that findings may be reproducible from centre to centre. One patient (Case 17), who was later to develop psoriasis, had been included in a large-scale therapeutic trial of cortisone compared with aspirin. He had been treated with cortisone and had done well. Retrospectively, it seems possible that this was because of the more favourable prognosis of psoriatic arthropathy rather than of the benefits of cortisone therapy. In retrospect also, there had been no firm way of differentiating his arthritis from that of rheumatoid arthritis, except the persistently negative S.C.A.T.

The history of the differentiation of the various forms of chronic polyarthritis dates from comparatively recent times. In a medical dictionary of 1825, arthritis and gout are tautologous (Hooper, 1825). Garrod (1876) established a concept of rheumatoid arthritis which still embraced other diseases. The 20th century has seen first the firm separation of proliferative or osteo-arthritis from atrophic or rheumatoid arthritis, and later the separation of ankylosing spondylitis from rheumatoid arthritis. Reiter's disease has emerged (Harkness, 1950) and has since merged with the chronic variety of post-venereal arthritis to establish a separate entity. With the widespread use of the S.C.A.T. as a reference, there have separated from the body of rheumatoid arthritis the concepts of psoriatic arthropathy, and the arthropathies of ulcerative colitis and erythema nodosum. Behçet's and Bazin's diseases, when they affect the joints, are now seldom thought to be varieties of rheumatoid arthritis. Two conditions appearing amongst the non-rheumatoid disorders which were discovered in this follow-up study (namely the aortitis associated with spondylitis, and reticulohistiocytosis) had not been fully characterized when the relevant patients in this study had first been observed. Thus it does not seem improbable that some of the polyarthritic disorders described in this paper, which are unlike typical rheumatoid arthritis, and have been associated with a persistently negative S.C.A.T., are examples of hitherto undescribed diseases. Further study has disclosed two further examples of the "middle-aged-female, severe-but-recovering, sero-negative, central-and-large-joint, polyarthritis" (see Cases 10 and 11), but clearly "four swallows do not make a summer" and more case reports are needed. Here, as in the estimation of other polyarthritic disorders, the S.C.A.T. will remain the touchstone of diagnosis.

Summary

61 out of 63 in-patients with severe, active polyarthritis, associated with a persistently negative sheep cell agglutination test (S.C.A.T.) for rheumatoid arthritis are reviewed. The average duration of follow-up was 5·4 years.

Of the 61 patients reviewed, twelve were found at follow-up to have developed a positive S.C.A.T. All but two of these had a distribution of arthritis typical of rheumatoid arthritis and six developed subcutaneous nodules. The course of their arthritis was not different from that seen in 23 patients in whom the arthritis was also typical but in whom the S.C.A.T. remained negative. Both mild and severe end-results were seen. A persistently negative

S.C.A.T. was compatible with typical rheumatoid arthritis of progressive course and fatal outcome.

Eleven patients had proven or probable diseases other than rheumatoid arthritis, these included gout, generalized osteo-arthritis, psoriatic arthropathy, reticulohistiocytosis, Takayushu's disease, Reiter's disease, and myelomatosis.

Eight patients showed a persistently negative S.C.A.T. and an atypical arthritis. The disease in these patients conformed to no accepted nosology and may have been examples of undescribed polyarthritic disorders. The evidence for this seemed strongest in two middle-aged females with severe and prolonged central and spinal polyarthritis associated with marked constitutional disease, proceeding to complete remission.

A reproducible diagnosis of rheumatoid arthritis requires a positive specific sheep cell agglutination test as well as clinical evidence of polyarthritis. In clinical studies of this disease the results of agglutination tests should be stated, and patients with persistently negative tests excluded or separately assessed.

I am indebted to various clinical colleagues, particularly Professor J. H. Kellgren and Dr. J. Sharp, for initial observations on these patients, and to Dr. J. Ball for the serological studies on which the selection of patients was based.

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"Arthrite rhumatismale" avec une réaction sérologique négative

RÉSUMÉ

On passe en revue 61 cas de polyarthrite évolutive grave, associée à une réaction d'agglutination des globules de mouton (*sheep cell agglutination test* = S.C.A.T.) constamment négative. Le temps moyen d'observation fut de 5,4 ans.

Sur ces 61 cas, douze d'entre eux développèrent au cours de la période d'observation une S.C.A.T. positive. Chez tous ces malades, sauf deux, la distribution de l'arthrite fut typique d'arthrite rhumatismale et six d'entre eux accusèrent des nodules souscutanés. L'évolution de leur arthrite ne se distinguait en rien de celle des 23 malades atteints d'une arthrite pas moins typique, mais chez qui la S.C.A.T. avait demeuré négative. On vit des résultats finaux graves et on en vit des benins. Une S.C.A.T. toujours négative fut compatible avec une arthrite rhumatismale typique d'un cours progressif menant à la mort.

Dans onze cas, des maladies autres que l'arthrite rhumatismale furent prouvées ou probables; parmi elles on trouva la goutte, l'ostéoarthrite généralisée, l'arthropathie psoriasique, la réticulohistiocytose, la maladie de Takayushu, la maladie de Reiter et la myelomatose.

Huit malades présentèrent une S.C.A.T. négative persistante avec une arthrite atypique. Ici la maladie ne correspondait à aucune entité nosologique et il pourrait s'y agir de désordres polyarthritiques non décrits auparavant. Ce groupe est caractérisé particulièrement par deux femmes d'un âge moyen, atteintes d'une polyarthrite centrale et vertébrale, grave et prolongée, associée à une maladie diathésique marquée, avec une évolution vers la rémission complète.

Un diagnostic ferme d'arthrite rhumatismale demande une S.C.A.T. spécifique positive en même temps que des signes de polyarthrite. Quand on étudie la pathologie de cette maladie, les résultats des réactions d'agglutination doivent être exprimés et les malades avec une réaction toujours négative doivent être exclus ou bien appréciés séparément.

"Artritis reumatoide" con reacción serológica negativa

SUMARIO

Se relatan 61 casos de poliartritis evolutiva grave, asociada con persistente negatividad de la reacción de aglutinación de los eritrocitos de carnero (*sheep cell agglutination test* = S.C.A.T.). El tiempo medio de observación fué de 5,4 años.

De estos 61 casos, doce desarrollaron durante el período de observación una S.C.A.T. positiva. En todos estos enfermos, excepto dos, la distribución de la artritis fué típica de artritis reumatoide y seis de ellos desarrollaron nódulos subcutáneos. La evolución de su artritis no presentó ninguna diferencia con la de 23 enfermos em los cuales la artritis fué también típica, pero en quienes la S.C.A.T. permaneció negativa. Se vieron tanto graves como leves resultados finales. Una S.C.A.T. siempre negativa fué compatible con una

artritis reumatoide típica de curso progresivo y terminación fatal.

En once casos enfermedades otras que la artritis reumatoide fueron comprobadas o probables; estas incluían gota, osteoartritis generalizada, artropatía psoriásica, reticulohistiocitosis, enfermedad de Takayushu, enfermedad de Reiter y mielomatosis.

Ocho enfermos presentaron una S.C.A.T. negativa persistente y artritis atípica. La enfermedad en estos pacientes no se adaptaba a ninguna determinada nosología y pueden haber sido ejemplos de desórdenes poliarticulares no descritos como entidad patológica. Los casos más evidentes de este grupo están representados por dos enfermas de edad media con grave y prolongada poliartritis central y vertebral, asociada con marcado defecto constitucional, que evolucionaron hacia la completa remisión.

Un diagnóstico reproducible de artritis reumatoide requiere específica reacción de aglutinación de los eritrocitos de carnero positiva a la vez que evidencia clínica de poliartritis. En los estudios clínicos sobre esta enfermedad, los resultados de dicha reacción deberían ser expresados y los enfermos con persistente reacción negativa excluidos o apreciados separadamente.

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EARLY DIAGNOSIS OF ARTHRITIS OF THE HAND

CLINICOPATHOLOGICAL STUDY OF SWOLLEN PAINFUL HANDS IN WOMEN OVER 40 YEARS OF AGE

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Swollen and painful joints in the hands of women over 40 years of age present a diagnostic problem. We have seen a number of patients whose signs and symptoms conformed to the criteria laid down by Kellgren and Moore (1952) for primary generalized osteo-arthritis but who, in addition, had swollen and painful metacarpophalangeal joints, particularly the second and third, and often involvement of the wrists. Frequently there was associated periarticular swelling.

In these cases the differential diagnosis between osteo-arthritis and rheumatoid arthritis on clinical, radiological, or serological grounds was extremely difficult.

The purpose of the present investigation was to determine to what extent biopsy of the small joints of the hand could contribute to an earlier diagnosis. Histological studies of joint tissue in rheumatoid arthritis and osteo-arthritis have mostly been confined to biopsy specimens from large joints or *post mortem* material. Early joint lesions in rheumatoid arthritis were described by Kulka, Bocking, Ropes, and Bauer (1955), using biopsy material from the knee joint. Cruickshank (1952), discussing changes in the synovial tissue in rheumatoid diseases, included the proximal interphalangeal joint, but we have been unable to find any reference to a series of biopsy studies of the small joints of the hand.

The present study was therefore concerned with three main problems:

(1) To find out whether biopsy of a small joint of the hand was a reasonable operative procedure, yielding sufficient suitable material.

(2) To find out whether the histological picture of the biopsy material could be correlated with the clinical picture of the patient at the time of biopsy or on follow-up.

(3) To assess the place of biopsy in the diagnosis of doubtful cases of arthritis of the hands.

Material

Thirty women who complained of pain and swelling of the hands with involvement of the second metacarpophalangeal joint were subjected to biopsy of this joint (Table, overleaf, pp. 234 and 235).

Three of these patients, all aged 38 to 39 years, had typical early rheumatoid arthritis (Cases 1-3). Symptoms had been present for less than 6 months, and the Rose-Waaler test was positive within 3 months of biopsy. They showed no radiological evidence of osteo-arthritis.

Three other patients aged 48 to 55 years, had uncomplicated generalized osteo-arthritis (Cases 22, 23 and 29).

In the remaining 24 patients, whose ages ranged from 40 to 75 years, certain features of both diseases were present. All had clinical evidence of osteo-arthritis, such as Heberden's nodes or thumb-base arthritis, together with radiographic evidence of degenerative joint changes. Constitutional symptoms were not marked and the erythrocyte sedimentation rate was not greatly raised.

In seven of these 24 patients (Cases 4 to 10), aged 42 to 71 years, a presumptive diagnosis of rheumatoid arthritis was made at the time of biopsy on the basis of the history and clinical findings alone in Cases 6 and 10, with the added evidence of the positive Rose-Waaler test in Cases 4, 8, and 9, and of joint erosions revealed by *x*-ray examination in Cases 4, 5, and 7.

In two other patients (Cases 25 and 27), a tentative diagnosis of osteo-arthritis was made.

In the remaining fifteen cases no diagnosis could be made at the time of biopsy.

Methods

Since needle biopsy of the second metacarpophalangeal joint had proved unsatisfactory an open approach was

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used. Biopsies were taken both under local and general anaesthesia. The second metacarpophalangeal joint was exposed from the dorso-medial aspect by incision of the skin and longitudinal splitting of the extensor tendon and joint capsule. A small piece of joint tissue and capsule was removed and the wound closed with interrupted sutures. No complications followed this procedure. Initially a dorso-lateral approach to the joint was employed, but this was abandoned because the extensor tendon could not be adequately secured and was liable to slip across the knuckle.

After fixation in 10 per cent. formol saline, the biopsy tissue was secondarily fixed in formol-sublimate before dehydration, clearing, and paraffin embedding. Haematoxylin and eosin stained sections were examined; additional stains used included Mallory's phosphotungstic acid haematoxylin, Orcein-Van Gieson's stain, a modified picro-Mallory technique, a modified Wilder's silver impregnation method for reticulin fibres, Azure A for mast cells, Trevan and Sharrock's method for plasma cells, and Perls' Prussian blue reaction for haemosiderin.

All sections were in the first instance examined by one of us without previous knowledge of the clinical findings.

Follow-up

All the patients have since been followed up for a minimum period of 9 months, the majority for over a year.

Histopathology

The following non-specific inflammatory changes in the biopsy material were regarded as consistent with a diagnosis of rheumatoid arthritis.

(1) Synovial hyperplasia.

(2) Proliferation of superficial synovial cells (synoviocytes).

(3) Increased vascularity and oedema of the subintimal layer.

(4) Marked lymphocytic and/or plasma cell infiltration of the subintima, either diffuse or with a tendency to form focal aggregations in swollen synovial villi.

These changes were seen in four of the other biopsies (Fig. 1, and Fig. 2, overleaf), but it should be empha-

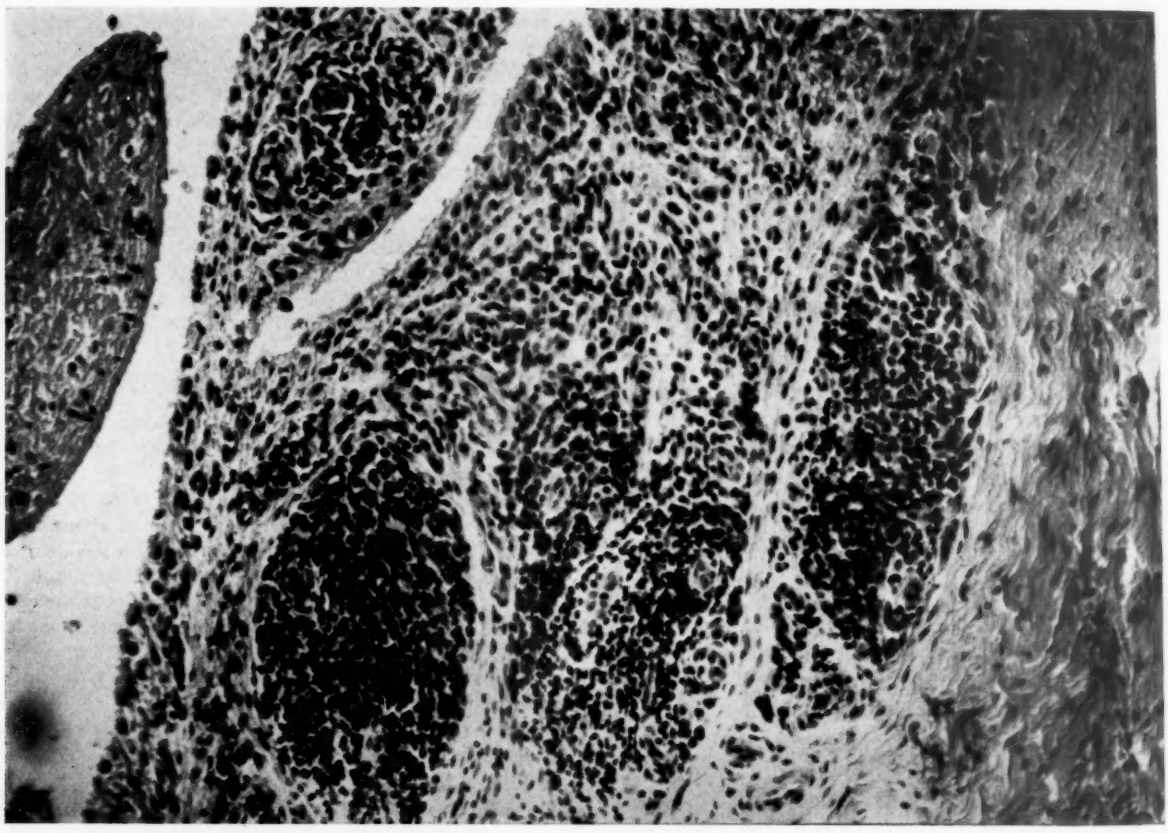

Fig. 1.—Case 7. Metacarpophalangeal joint capsule showing swollen synovium heavily infiltrated with lymphocytes and plasma cells. Surface fibrinous exudate on left.
Haematoxylin and eosin. ×160.

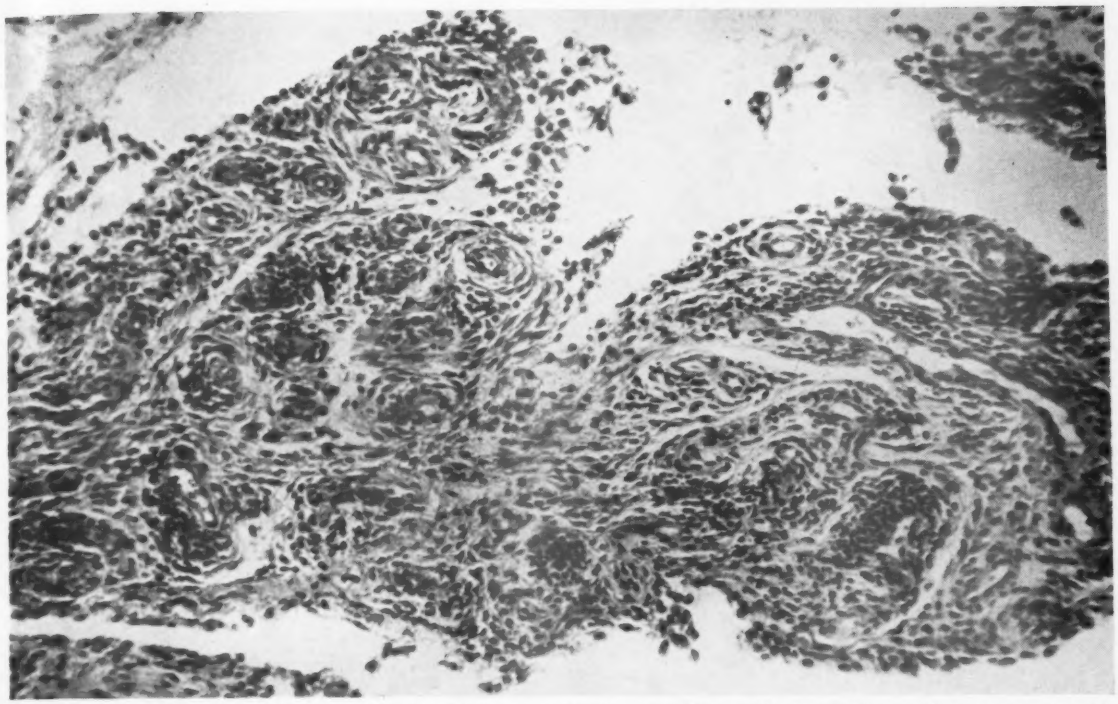

Fig. 2.—Case 5. Thickened synovial villus showing patchy synoviocytic hyperplasia with increased vascularization and moderate lymphocytic and plasma cell infiltration of the sub-intima. Perivascular cellular cuffing is present. Haematoxylin and eosin. ×93.

sized that the flamboyant massive cellular infiltration with profusion of lymphoid follicles seen in biopsies of larger joints in some cases of rheumatoid disease was never observed in the present series. In three of these cases fibrinous exudate was deposited on the synovial surface. All four biopsies showed moderate numbers of mast cells in the subintimal, cellular infiltrate. The mast cells were present round the small blood vessels and in the loose areolar tissue. In some areas these cells had infiltrated the overlying synoviocytic layer.

Small granulomatous foci with fibrinoid deposition were seen in the fibrous capsule of the joint in two other biopsies (Fig. 3, overleaf). In the affected areas the normal dense fibrous tissue of the stratum fibrosum was replaced by highly vascular inflammatory tissue, containing numerous newly-formed capillaries and variable numbers of lymphocytes, plasma cells, histiocytes, polymorphs, and fibroblasts. Strongly fuchsinophilic fibrinoid material was deposited adjacent to the microgranulomata, and in both the vascular and necrotic foci the normal collagen structure had been disrupted or obliterated. We regarded the presence of these capsular lesions as compatible with the diagnosis of rheumatoid disease, although the foci lacked the structure of a typical rheumatoid nodule and the overlying stratum synoviale showed only a mild inflammatory reaction.

Eight of the remaining 24 biopsies showed definite evidence of a synovitis. The inflammatory reaction was insufficiently florid to justify a definite histological diagnosis of rheumatoid arthritis (Fig. 4, overleaf), but they all presented some of the above-mentioned features.

One biopsy (Case 11) showed a copious fibrinocellular surface exudate, obliteration of the synovial layer, and an intense acute inflammatory reaction containing numerous polymorphs in the thickened highly vascular subintima (Fig. 5, overleaf). No bacteria were seen and the picture was compatible with an acute synovitis. Subsequent follow-up suggested that the lesion was an acute form of early rheumatoid synovitis.

The other fourteen biopsies showed no evidence of an active synovitis. Distinction between normality or minor degrees of synovial degeneration and fibrosis was not always clear.

Thirteen of the 24 biopsies showed partial transformation of the synoviocytic and subintimal layers into hypocellular, avascular tissue that in some sections closely resembled fibrocartilage (Fig. 6, overleaf). Various transitional forms between typical synovial tissue and typical cartilage were seen,

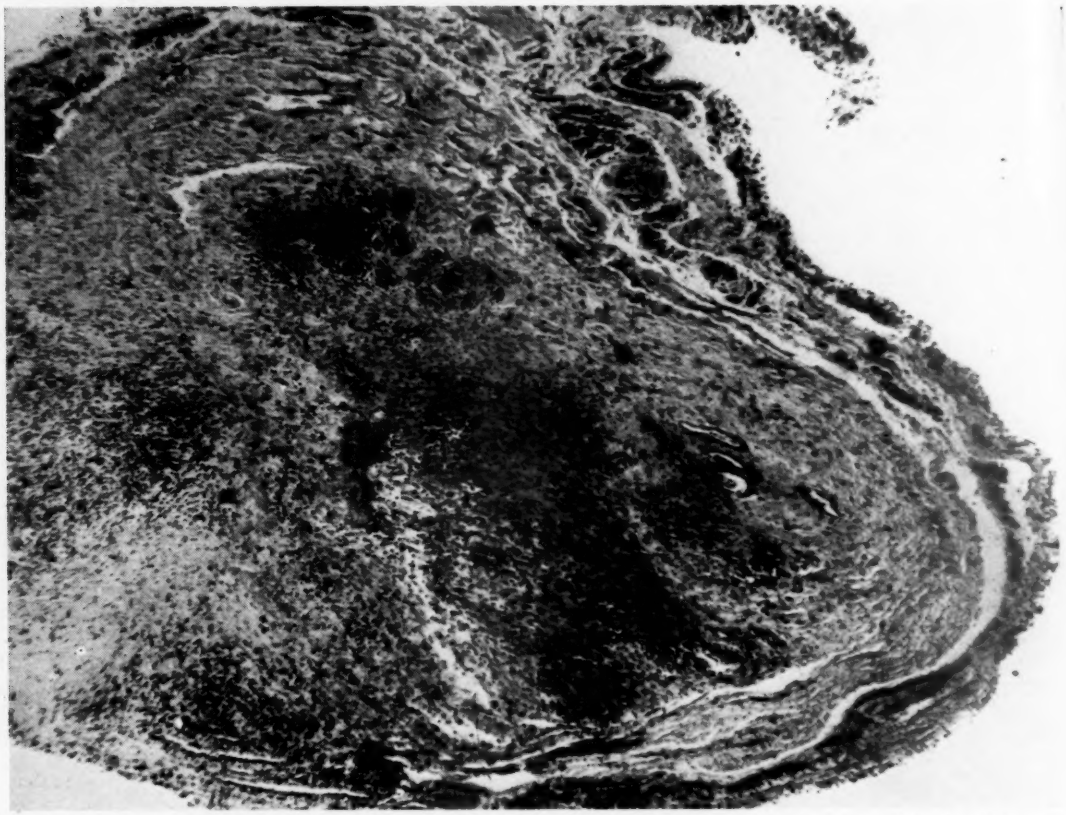

Fig. 3.—Case 6. Darkly stained microgranulomata in fibrous capsule of metacarpophalangeal joint. Minimal cellular reaction in stratum synoviale on right.
Haematoxylin and eosin. ×37.

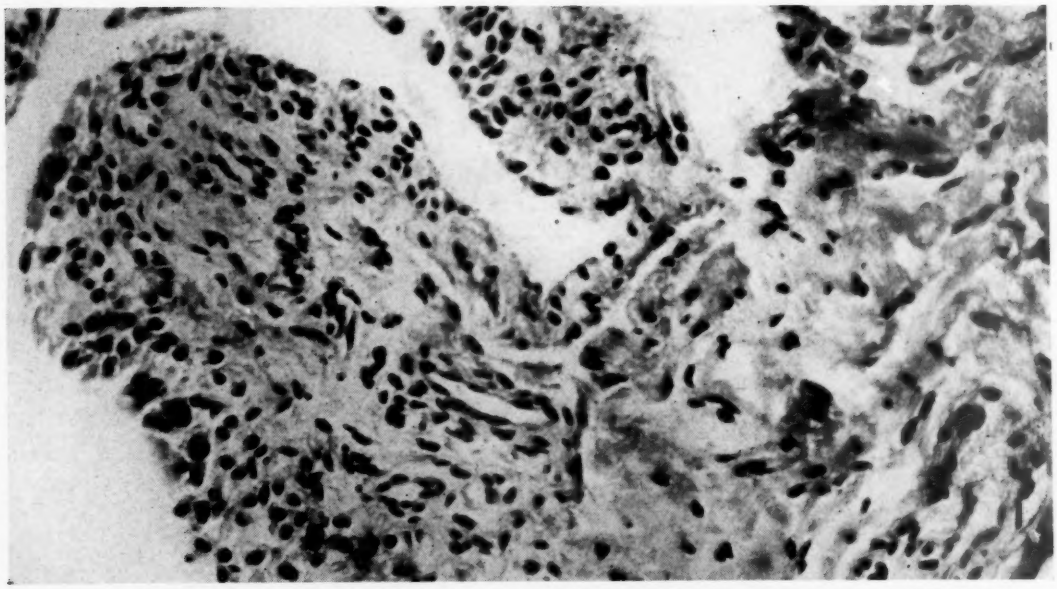

Fig. 4.—Case 12. Mild synovial hyperplasia with light chronic non-specific inflammatory reaction in sub-intima.
Haematoxylin and eosin. ×206.

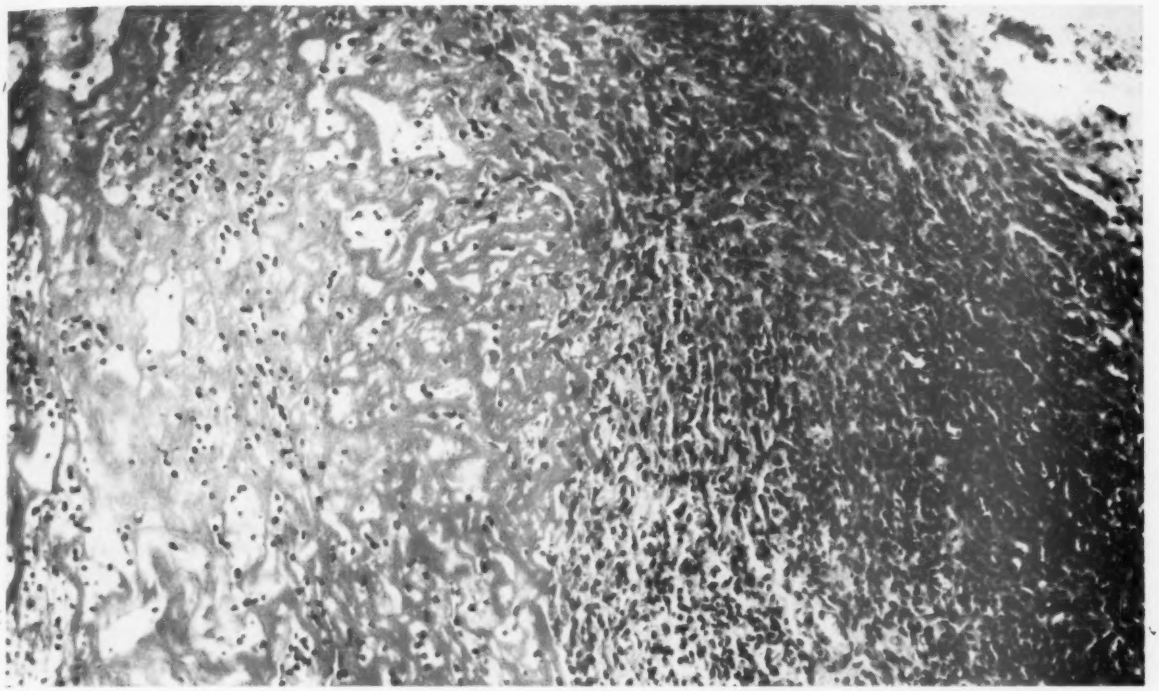

Fig. 5.—Case 11. Acute inflammatory changes in stratum synoviale with fibrino-cellular surface exudate on left. Haematoxylin and eosin. ×93.

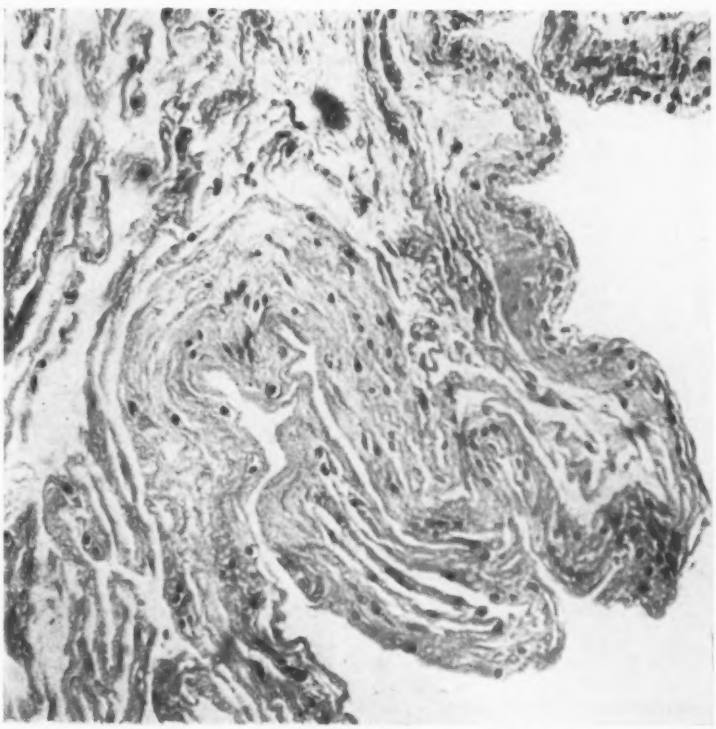

Fig. 6.—Case 22. Synovium denuded of surface cells and showing devascularization of subsynovial tissue with chondroid metaplasia. Haematoxylin and eosin. ×80.

and in some specimens this chondroid metaplasia was quite striking.

One remaining biopsy consisted of a small fragment of fibrous tissue devoid of synovia and was considered inadequate for histological diagnosis.

In several specimens the small arteries showed medial hypertrophy and subintimal thickening, but fibrinoid necrosis of the arterial wall was observed in one case only. Subintimal pericapillary fibrosis was a common finding.

The biopsies were very small in several cases which showed little or no inflammatory activity. This was regarded initially as an error of technique, but it was later appreciated that such synovial specimens were either normal or atrophic in contrast to the relatively abundant tissue available for sectioning from cases with active inflammatory lesions.

None of the biopsies showed histological evidence of tuberculosis or gout.

The thirty cases were classified on histological evidence as follows (Table):

Group 1: Six showing changes consistent with a diagnosis of rheumatoid arthritis (Cases 2, 4, 5, 6, 7, 13) and one (Group 1a) with acute synovitis (Case 11).

Group 2: Eight showing evidence of chronic synovitis but with changes too slight to justify a definite diagnosis of rheumatoid arthritis (Cases 1, 3, 8, 9, 10, 12, 14, 17).

Group 3: Fourteen showing minimal inflammatory changes, fibrosis, and degeneration, or with normal tissue (Cases 15, 16, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29).

Group 4: One in which the tissue obtained at biopsy was insufficient for diagnosis (Case 30).

Clinico-Pathological Correlation

It was pointed out by Cruickshank (1952), in his study of consecutive biopsies from larger joints, that a single specimen might not show the full inflammatory picture and that biopsies from different areas of the same joint often showed widely differing pathological states. We were therefore surprised to find that the pathological picture from a single biopsy of a small joint could be correlated with the clinical diagnosis.

As a result of the follow-up of our cases, a clinical diagnosis has been reached in all but three. When the diagnosis is compared with the histological findings it appears that evidence of some inflammatory change in the synovia corresponds with the rheumatoid arthritis group, whereas absence of inflammatory change or normal synovia is found in the group with osteo-arthritis.

Although no case showed the classical foci of rheumatoid arthritis described by Allison and Ghormley (1931), there was sufficient evidence in seven of the biopsy specimens to justify a histological diagnosis of rheumatoid arthritis. In this series it appears that the presence of a milder degree of synovitis was also associated with rheumatoid arthritis, but, as might be expected, the degree of histological change was not related to the severity of the clinical picture. Of the three cases of typical early acute rheumatoid arthritis used as "controls", one showed marked inflammatory changes in the synovia, and the other two only

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CLINICAL AND PATHOLOGICAL FINDINGS

Case No.	Age (yrs)	Diagnosis			Clinical Symptoms		
		Past History Suggestive of:	Provisional Diagnosis at Biopsy	Diagnosis on Follow-up	Morning Stiffness for More or Less than 30 min.	Periarticular Swelling	Wrist Swelling
1	38	Nil	RA	RA	+	+	—
2	39	Nil	RA	RA	+	+	+
3	38	Nil	RA	RA	—	+	—
4	45	RA	RA	RA	+	+	+
5†	60	RA†	RA	RA	+	+	+
6‡	58	RA‡	RA	RA	+	+	—
7*	71	RA*	RA	RA	+	+	—
8	42	RA	RA	RA	—	+	—
9	47	RA	RA	RA	+	—	—
10	43	RA	RA	RA	—	—	—
11‖	65	OA	?‖	RA	—	+	+
12§	45	?	?§	RA	+	+	+
13	45	?	?	RA	—	+	+
14	40	?	?	RA	+	+	+
15	56	?	?	?	—	+	—
16	68	?	?	?	+	+	—
17	71	OA	?	?	+	—	+
18	62	?	?	OA	—	—	+
19	57	RA	?	OA	—	—	—
20	44	RA	?	OA	+	—	—
21	52	?	?	OA	—	+	—
22**	48	OA	OA**	OA	—	—	—
23	55	OA	OA	OA	+	—	—
24	67	OA	?	OA	—	—	—
25	71	OA	OA	OA	—	—	+
26	56	OA	?	OA	—	+	—
27	75	OA	OA	OA	+	—	—
28	58	?	?	OA	+	—	+
29	52	OA	OA	OA	—	—	—
30	58	?	?	OA	—	—	+

RA = Rheumatoid Arthritis
OA = Osteo-arthritis

* Fig. 1. † Fig. 2. ‡ Fig. 3. § Fig. 4. ‖ Fig. 5. ** Fig. 6.

mild synovitis. On the whole, however, there was a tendency for cases in which a diagnosis of rheumatoid arthritis was considered most likely at the time of biopsy to show a more florid histological picture.

Moderate numbers of mast cells in the inflammatory cellular infiltrate in rheumatoid synovitis has rarely been recorded; Kulka and others (1955) briefly mentioned their presence in one of a series of synovial biopsies from knee joints in cases of early rheumatoid arthritis. However, it is unlikely that this observation has any special diagnostic significance.

Previous work on the pathological changes in the joints in osteo-arthritis has stressed the relative absence of inflammatory changes in synovial tissue (Collins, 1949). Nevertheless, we were surprised to find normal or even atrophic synovia in joints which were clinically swollen and painful. However, the absence of inflammatory changes appeared to be of considerable diagnostic significance, since none of these patients has developed a clinical picture of rheumatoid disease during follow-up.

A fairly high proportion of biopsies showing some degree of chondroid transformation of the synovial layer was noted. It is possible that such metaplasia is associated with a degenerative or atrophic process occurring in the mesenchymal elements of the synovia, although, according to Maximow and Bloom (1957), small amounts of cartilage and all transitions between cartilage cells and joint or synovial cells can be found occasionally in normal diarthrodial joints. Much has been written about the arterial changes in rheumatoid arthritis (Cruickshank, 1954; Ball, 1954; Kulka and others, 1955; Clark, Kulka, and Bauer, 1957; Bywaters, 1957; Kellgren and Ball, 1959), but there is no great measure of agreement about their nature or significance. In our patients there were changes in the small arteries (medial hypertrophy, subintimal thickening) and in the capillaries (pericapillary fibrosis) in a number of cases, but, although they were rather more common in the group with active synovitis (twelve out of fifteen cases), such changes were seen together with normal or quiescent synovia in five out of fourteen cases.

In some sections, concentric intimal thickening of the arterioles was seen. These changes were not unlike those described by Whiteley and Wilson (1952); Wade and Ball (1957); Bywaters (1957); and

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IN THIRTY PATIENTS SUBMITTED TO BIOPSY

Radiology			Laboratory Tests		
Porosis	Erosions	Sclerosis	Rose-Waaler Test	Highest Erythrocyte Sedimentation Rate (mm./hr; Westergren)	Biopsy Group
+	—	—	+	12	2
+	—	—	—+	57	1
+	—	—	—+	45	2
+	+	+	+	25	1
+	+	—	—	32	1
+	—	+	—+	29	1
+	+	+	—	18	1
—	—	+	+	23	2
+	—	+	+	29	2
+	—	+	—	13	2
+	—	+	—+	37	1a
—	—	+	—	27	2
—	—	+	—	23	1
—	—	—	—	7	2
—	—	+	—	10	3
—	—	+	—	7	3
—	—	+	—	26	2
—	—	+	—	20	3
—	—	+	+—	20	3
—	—	—	+—	15	3
—	—	+	—	6	3
—	—	+	—	17	3
—	—	+	—	10	3
—	—	+	—	14	3
—	—	+	—	40	3
+	—	+	—	12	3
—	—	+	—	7	3
—	—	+	—	38	3
—	—	+	—	10	3
—	—	+	—	26	4

Rose-Waaler Test —+ = Negative at biopsy; later positive
+— = Positive before biopsy; negative at biopsy

Kellgren and Ball (1959), to which the name fibroelastosis has been given. But it should be stated that the biopsies in our series were not processed or examined with the particular object of studying vascular lesions.

When we compared the clinical findings at the time of biopsy with the histological picture in the light of the final diagnosis, certain clinical features appeared to be particularly important in the diagnosis of rheumatoid arthritis. Morning stiffness for more than 30 minutes was present in nine of fourteen cases in the rheumatoid group, but in only four of the thirteen cases in the osteo-arthritic group. Severe periarticular swelling with transmetacarpal tenderness was also found to vary in the two groups in the same proportions.

Although a history suggestive of rheumatoid arthritis in the past was helpful in the majority of cases, in two cases it was misleading. Both patients had a previous history of rheumatoid disease with a positive Rose-Waaler test, one having received steroid therapy. At the time of biopsy the Rose-Waaler test was negative and the clinical diagnosis was in doubt. Biopsy specimens from these patients showed inactive synovial tissue, and neither exhibited any further clinical evidence of rheumatoid arthritis.

Discussion

Although there have been striking advances in the diagnosis and treatment of rheumatoid arthritis in the last 20 years, the exact definition in many early cases remains obscure. The introduction of serological tests has assisted the diagnosis of rheumatoid disease, but in osteo-arthritis there is very little laboratory aid. Serological tests, however, do not necessarily differentiate the early stages of illness, when the overlap of signs and symptoms makes accurate clinical diagnosis impossible.

In women over 40 years of age, degenerative changes in the joints of the hands are frequently present, together with Heberden's nodes. While these are suggestive of osteo-arthritis, their presence does not exclude rheumatoid disease, nor does a past history of rheumatoid arthritis prevent the onset of primary generalized osteo-arthritis. Systemic or constitutional symptoms are not marked in primary generalized osteo-arthritis, nor often in the early stages of rheumatoid arthritis, but menopausal symptoms occurring in either group may add to the confusion.

Cecil and Archer (1925, 1926) classified 145 of 182 cases of degenerative arthritis as "arthritis of the menopause". Though this term proved to be ill-chosen, in so far as later work failed to show a definite correlation between endocrine changes and the development of osteo-arthritis, it focused attention on the great problem of arthritis occurring initially in middle-aged women.

Although, in the majority of cases, a clinical diagnosis can be made after a period of observation, the importance of early accurate diagnosis lies in the different treatment and prognosis of the two conditions. Duthie, Thompson, Weir, and Fletcher (1955) have shown that patients with rheumatoid arthritis do better if they receive intensive treatment, preferably in hospital, in the early stages of the disease. Early treatment leads to a quicker return to normal life with a smaller chance of relapse and permanent crippling. On the other hand, Kellgren and Moore (1952) found that, in their cases of osteo-arthritis, although there was a certain amount of deformity, permanent crippling very seldom occurred and the disease tended to run a self-limiting and benign course.

The study of a relatively small number of cases has shown that open biopsy is a reasonably safe procedure, and that sufficient material can usually be obtained for histological study. There have been no permanent complications, although transient attacks of pain and stiffness in the biopsied joint occurred in a number of patients. The patient whose specimen showed acute synovitis developed an effusion into the joint 4 months after biopsy when there was a general exacerbation of the rheumatoid process, but with intra-articular hydrocortisone therapy the effusion resolved without further complications.

The majority of patients in whom the synovial tissue showed evidence of inflammatory changes, though these were often mild, subsequently developed the clinical features of rheumatoid arthritis. We therefore felt that it would be justifiable to treat these patients as cases of rheumatoid arthritis on the basis of the histological findings. On the other hand, the patients without evidence of synovial inflammation appeared to be suffering from primary generalized osteo-arthritis; the pain and swelling of the joint being probably due to soft tissue swelling, associated with mucoid degeneration of the connective tissue. This change is thought to precede the new bone formation in Heberden's nodes (Collins, 1949).

Six cases in the rheumatoid group had a persistently negative Rose-Waaler test; in those in whom the clinical course was benign, the differential diagnosis between an evanescent attack of rheumatoid arthritis and acute osteo-arthritis could only have been made at an earlier stage on histological evidence.

Conclusion

Within the limitations of a small series and a relatively short period of follow-up, biopsy of the second metacarpophalangeal joint has been found useful in the differential diagnosis of the painful swollen hand, where this could not be made on clinical, serological, and radiological evidence.

Although there were no complications, biopsy is not advocated as a routine measure, but should be considered in the following circumstances:

(1) When a rheumatoid process may be superimposed on degenerative changes.
(2) When the pattern of joint involvement is not characteristic.
(3) When serological tests and *x* rays are unhelpful.
(4) When the line of treatment is doubtful.

From the results of this series two main groups of patients emerge:

(*a*) That in which the biopsy specimen shows evidence of inflammatory changes. Clinically the majority of these patients showed evidence of rheumatoid arthritis, either at the time of biopsy or on follow-up. It is suggested that all such cases should be treated as cases of rheumatoid arthritis.

(*b*) That in which the biopsy specimen showed normal or inactive synovial tissue. None of these patients developed rheumatoid arthritis on follow-up, and they were thought to be suffering from primary generalized osteo-arthritis, requiring supportive therapy and reassurance.

Clinical features which correlated well with the pathological findings were morning stiffness for more than 30 minutes and marked periarticular swelling. It was not possible to distinguish histologically between serologically positive and negative cases of rheumatoid arthritis. Two patients with a past history of serologically positive rheumatoid disease showed quiescent synovia, indistinguishable from that seen in osteo-arthritis.

Summary

Thirty women presenting with pain and swelling of the hands submitted to biopsy of the second metacarpophalangeal joint of one hand.

The problems of differential diagnosis between rheumatoid arthritis and osteo-arthritis in patients over 40 years of age are discussed. The technique of biopsy of the second metacarpophalangeal joint is described and the results correlated with the clinical features both at the time of biopsy and at follow-up.

Histologically, the specimens were divided into two main groups: those showing inflammatory changes in the synovia and those with normal or atrophic tissue. Patients with rheumatoid arthritis showed inflammatory changes in the synovial tissue, whereas there was no evidence of inflammation in the synovia of osteo-arthritic patients.

Follow-up for over one year showed that none of the patients with uninflamed synovia subsequently developed rheumatoid arthritis.

In view of these findings it is suggested that biopsy of the second metacarpophalangeal joint in certain circumstances could be a valuable guide to early diagnosis.

Our thanks are due to Dr. A. T. Richardson for his valuable advice and encouragement, and permission to use his cases, and to Prof. K. R. Hill for kind permission to use his laboratory facilities. We are also indebted to Mr. J. A. Turner for helping to devise the biopsy technique, to Mr. R. R. Phillips for the photomicroscopy, and to Mr. G. Humblestone for technical assistance.

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Diagnostic précoce de l'arthrite de la main.—Etude clinique et pathologique des mains douloureuses et tuméfiées des femmes âgées de plus de 40 ans

RÉSUMÉ

On procéda, chez trente femmes aux mains tuméfiées et douloureuses, à des biopsies de la deuxième articulation métacarpo-phalangienne d'une main.

On discute le problème de diagnostic différentiel entre l'arthrite rhumatismale et l'ostéoarthrite chez des femmes âgées de plus de 40 ans. On décrit la technique de la biopsie de la deuxième articulation métacarpo-phalangienne et on met en correlation les résultats avec le tableau clinique au temps de la biopsie et pendant une période d'observation subséquente.

Histologiquement, on divise les prélèvements en deux groupes: l'un portant des signes d'inflammation synoviale et l'autre caractérisé par des tissus normaux ou atrophiques. Les malades atteints d'arthrite rhumatismale accusent des altérations inflammatoires de la membrane synoviale, tandis que des signes d'une telle inflammation sont absents dans l'ostéoarthrite.

L'observation pendant plus d'un an montre que les malades à la membrane synoviale non-inflammée ne sont pas frappés par l'arthrite rhumatismale.

En vue de ces résultats on suggère qu'une biopsie de la deuxième articulation métacarpo-phalangienne, en certaines circonstances, peut être un guide utile pour le diagnostic précoce.

Diagnóstico precoz de la artritis de la mano.—Estudio clínico-patológico de manos hinchadas y dolorosas en mujeres de edad superior a 40 años

SUMARIO

Treinta mujeres con dolor e hinchazón de las manos fueron sometidas a biopsia de la segunda articulación metacarpo-falangiana de una mano.

Se discuten los problemas de diagnóstico diferencial entre artritis reumatoide y ósteo-artritis en enfermos de más de 40 años de edad. Se describe la técnica de la biopsia de la segunda articulación metacarpo-falangiana y los resultados se relacionan con el cuadro clínico en el momento de la biopsia y durante el período posterior de observación.

Histológicamente, el material se divide en dos grupos: uno con cambios inflamatorios de la sinovia y el otro con tejidos normales o atróficos. Los enfermos con artritis reumatoide presentan alteraciones inflamatorias de la membrana sinovial, mientras que no existe evidencia de inflamación en la sinovia de los enfermos con ósteo-artritis.

La observación continuada de los enfermos por más de un año demuestra que ninguno de aquellos que no presentaron inflamación sinovial desarrolla posteriormente artritis reumatoide.

En vista de los resultados se sugiere que la biopsia de la segunda articulación metacarpo-falangiana puede ser, en determinadas circunstancias, una guia de valor en el diagnóstico precoz.

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OBSERVATIONS ON THE ULTRACENTRIFUGAL PATTERN OF SERUM PROTEINS IN RHEUMATOID ARTHRITIS

BY

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Recent evidence has demonstrated that the serum protein alterations commonly present in rheumatoid arthritis, though following the general pattern of chronic infectious diseases (that is hypoalbuminaemia, hyperalpha- and hypergamma-globulinaemia), show some distinctive features that may be specific for this disease. The most evident among these features is the presence of globulins with a high sedimentation constant ($S_{w,20} \cong 22$) (Franklin, Holman, Müller-Eberhard, and Kunkel, 1957; Kuhn, 1959); it is believed that the 22S fraction derives from the association of a globulin of the normal 7S class with a protein macromolecule (19S) that is responsible for the serological reactions termed collectively the rheumatoid factor (Franklin and Kunkel, 1958; Kunkel, Franklin, and Müller-Eberhard, 1959; Vaughan, 1959). A close relation between the level of this component and the severity of the clinical picture has been observed (Franklin, Kunkel, and Ward, 1958; Kuhn, 1959). The exact significance of this fraction in the pathology of rheumatoid arthritis is still unknown; it has been suggested that it may play a role in determining vascular and perivascular lesions that are an essential feature of the disease (Christian, 1958; Epstein and Engleman, 1959); furthermore, its precipitation in tissues, as a consequence of an immunological reaction, may have a pathogenic role (Franklin, Kunkel, and Ward, 1958; Kunkel, 1959; Vaughan and Orbison, 1959). However, these hypotheses are far from being substantiated by direct evidence and a more detailed knowledge of the protein pattern in this disease seems to be necessary before an interpretation is attempted.

Data obtained in our Department (Salteri, Cirla, and Fasoli, 1960) in patients with acute exacerbations of rheumatoid arthritis corresponding to the picture of the "aggravation syndrome" that often develops after prolonged steroid treatment (Villa, Ballabio, and Sala, 1953; Ballabio and Grampa, 1960), may contribute to the characterization of the protein pattern of this disease.

Material and Methods

Fifteen patients with the clinical picture of rheumatoid arthritis according to current criteria have been studied: eleven showed the usual signs of the disease in its fully developed form and four presented the symptoms of the "aggravation syndrome".

Serum samples, obtained in the post-absorptive state, were diluted with normal saline to a protein content of 1-3 g. per cent. and analysed in the Spinco Model E Ultracentrifuge, at room temperature (about 20° C.), at 52,640 r.p.m. Photographs were taken at 16-min. intervals after the rotor reached full speed. The pictures were enlarged and the areas of the various peaks determined with a planimeter. The S values were calculated according to the usual formula, by extrapolating to zero concentration the values observed for the same samples at various dilutions.

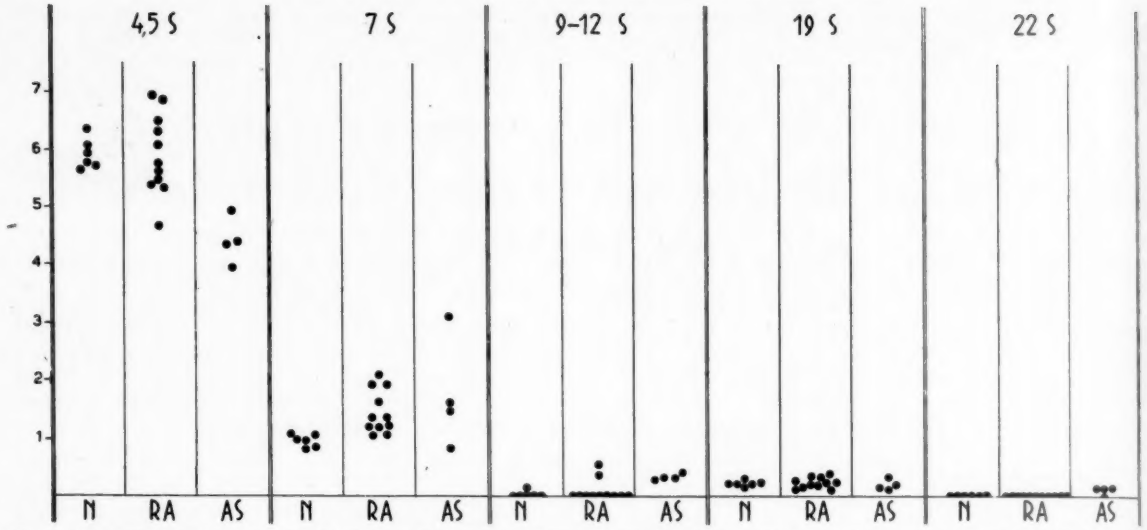

Fig. 1.—Ultracentrifugal serum protein fractions in normal subjects (N) and in patients with rheumatoid arthritis in the typical form (R.A.) and with the "aggravation syndrome" (A.S.).

Results

(A) Typical Rheumatoid Arthritis (Fig. 1)

The ultracentrifugal analysis of serum proteins does not show in most cases specific abnormalities: there is a moderate increase of the 7S fraction, and an inconstant tendency towards a diminution of the 4·5S fraction, while the 19S component is well within the normal range of variation. This picture corresponds, as a whole, to that of other chronic inflammatory diseases.

However, in two cases in this group another peak was present, close to the descending branch of the 7S peak, that corresponded to an S value of 9-12 and to a concentration of 0·3-0·5 g. per cent. (Fig. 2, opposite). This component is not evident with this technique (or is present only in trivial amounts) in the rest of the sera of the group, and in the conditions involving hyperglobulinaemia that have been studied so far, with the exception of some cases of plasmocytoma.

(B) Rheumatoid Arthritis with "Aggravation Syndrome" (Fig. 1)

The four cases in this group show a lower level of the 4·5S fraction than the preceding series, and no clear-cut differences exist with regard to the 7S and 19S components. All show relatively large amounts of the 9-12S fraction (0·2-0·5 g. per cent.), and three also have a 22S component of 0·1-0·15 g. per cent. (Fig. 3, opposite).

In three cases the analysis was repeated 1 to 4 months later, after a period of treatment with high doses of ACTH and with prednisone at a lower dose level than before admission. Two patients experienced a marked clinical improvement and, at the same time, showed an amelioration of the protein pattern—an increase of the 4·5S fraction and a decrease of the 7S and 9-12S fractions; the 22S component did not change to a significant degree. The third patient did not improve either clinically or with regard to the serum protein picture (Table).

TABLE

CHANGES IN THE ULTRACENTRIFUGAL SERUM PROTEIN FRACTIONS IN THREE RHEUMATOID ARTHRITIC PATIENTS WITH "AGGRAVATION SYNDROME" AFTER TREATMENT WITH ACTH AND LOW DOSES OF PREDNISONE

Case No.		Protein Fractions (g. per cent.)				
		4·5S	7S	9-12S	19S	22S
1	Before	4·40	1·51	0·33	0·14	0·12
	After	4·31	0·81	0·20	0·07	0·11
2	Before	4·96	1·68	0·31	0·20	0·15
	After	5·41	0·85	—	0·21	0·13
3	Before	4·43	0·86	0·37	0·34	—
	After	4·59	0·61	0·52	0·38	—

Discussion

Our data correspond in general to the results obtained by other authors: however, they differ in showing the occasional presence of a 9-12S

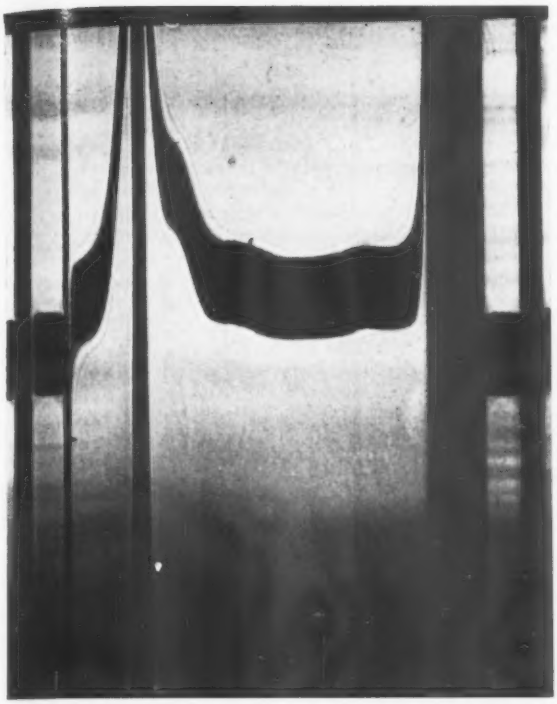

Fig. 2.—Photograph taken after 64 min. ultracentrifugation at 52,640 r.p.m. (bar angle 70°) of the serum (diluted 1 : 3 with normal saline) of a patient with typical rheumatoid arthritis. The following peaks are visible from left to right: 4·5S, 7S, 10S, and 19S.

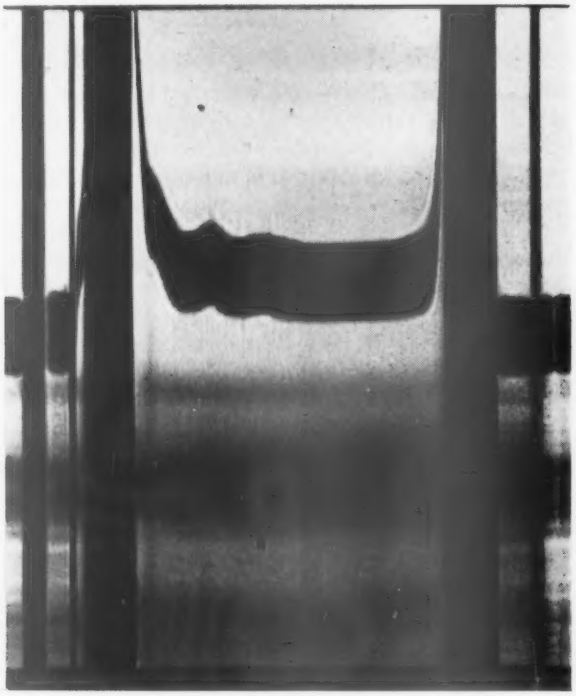

Fig. 3.—Photograph taken after 32 min. ultracentrifugation at 52,640 r.p.m. (bar angle 70°) of the serum (diluted 1 : 2 with normal saline) of a patient with the "aggravation syndrome". On the descending branch of the main peak (4·5 + 7S) it is possible to recognize the 10S component; to the right of this the 19S and 22S peaks are seen.

fraction in patients with typical rheumatoid arthritis and in all cases of our series with the "aggravation syndrome". A fraction with similar sedimentation characteristics has been observed in trace amounts by Wallenius, Trautman, Kunkel, and Franklin (1957) in their ultracentrifugal studies of the electrophoretic components of normal human serum; it was seen that both the alpha$_2$ and beta globulins contained a small amount of material with an S value of 12. Christian (1959) has presented data suggesting that cold precipitates from rheumatoid arthritic sera may contain a component with an S value between 7 and 19.

Our data show that the level of the 9-12S component may be related to the severity of the rheumatoid arthritis symptoms, particularly in cases with the "aggravation syndrome".

In three of our cases a 22S fraction was present; our data are not sufficient to rule out a possible relation between the level of this fraction and that of the 9-12S component; however, they suggest that this is not the case, though both changes are often present at the same time.

It is noteworthy, on the whole, that rheumatoid arthritis is associated with serum protein changes that are rarely, if ever, present in other related or unrelated conditions; the presence in plasmocytoma or macroglobulinaemia of fractions having a sedimentation constant of the same order of magnitude as that of the two above-mentioned components observed in rheumatoid arthritis (9-12S and 22S) does not imply the chemical and/or biological identity of the fractions showing the same S values.

The tendency of rheumatoid arthritic patients to build up protein components that differ in sedimentation rate (and therefore in molecular weight) from the normal may indicate either a derangement of serum protein synthesis or the interaction of normal protein with other substances or with one another so that a larger particle is formed. Some data suggest that the latter mechanism is possibly the one responsible.

No data are available on the origin of the 9-12S component of rheumatoid arthritis; the possibility that it may derive from the interaction of normal components cannot be ruled out. The fact that a fraction with similar characteristics has been shown to be present, in minimal amount, in normal sera would suggest that it is related to this normal component. Obviously new evidence is necessary to clarify this question.

Summary

Ultracentrifugal analysis of serum proteins was performed in fifteen patients with rheumatoid arthritis. In eleven cases the disease had a typical course, and in four who had been treated with long-term steroid therapy the clinical picture of the so-called "aggravation syndrome" was present. In the former group the serum protein pattern showed a moderate rise of the 7S fraction as the most constant abnormality; in two cases a peak in the 9-12S region was observed. In the latter group (those with the "aggravation syndrome") a consistent diminution of the 4·5S fraction was recorded in addition to the rise of the 7S fraction. The 9-12S peak was evident in all cases, of the "aggravation syndrome" and in three of them a 22S component was also present.

The amelioration of the clinical picture was associated with a rise of the 4·5S fraction and a diminution of the 7S and 9-12S components.

The possible meaning of these findings for the pathological physiology of rheumatoid arthritis is tentatively discussed.

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Observations sur l'image ultracentrifuge des protéines du sérum dans l'arthrite rhumatismale

RÉSUMÉ

On analysa par centrifugation les protéines sériques de 15 malades atteints d'arthrite rhumatismale. Dans 11 cas la maladie présentait une évolution typique, mais chez 4 malades, traités pendant un temps prolongé par des stéroïdes, il y avait un tableau clinique nommé "syndrome d'aggravation". Dans le premier groupe on nota une élévation modérée de la fraction 7S comme la plus constante anomalie; dans deux cas on observa un sommet dans la région 9-12S. Dans le deuxième groupe (celui avec la "syndrome d'aggravation") il y eut une diminution régulière de la fraction 4·5S, en même temps qu'une augmentation de la fraction 7S. Le sommet 9-12S fut évident dans tous les cas de "syndrome d'aggravation" et dans trois d'entre eux il y eut aussi un composant 22S.

Une amélioration du tableau clinique fut associée à une élévation de la fraction 4·5S et une baisse des composants 7S et 9-12S.

On discute tentativement la possible importance de ces données dans la physiopathologie de l'arthrite rhumatismale.

Observaciones sobre el proteinograma sérico por ultracentifugación en la artritis reumatoide

SUMARIO

Se realizó un análisis por ultracentrifugación de las proteinas séricas de 15 enfermos con artritis reumatoide. En once casos la enfermedad presentaba un curso típico, y en cuatro enfermos, tratados durante un largo tiempo con esteroides, estaba presente un cuadro clínico del llamado "síndrome de agravación". En el primer grupo se notó una moderada elevación de la fracción 7S como la anormalidad más constante; en dos casos se observó una cima en la zona 9-12S. En el segundo grupo (aquél con "síndrome de agravación") se presentó una coherente disminución de la fracción 4·5S, al mismo tiempo que la elevación de la fracción 7S. La cima 9-12S fué evidente en todos los casos con "síndrome de agravación" y en tres de ellos un componente 22S estuvo presente también.

La mejoría del cuadro clínico se vió asociada con una elevación de la fracción 4·5S y una disminución de los componentes 7S y 9-12S.

Se discute tentativamente el posible significado de estos hallazgos en la fisiopatologia de la artritis reumatoide.

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CHLOROQUINE IN RHEUMATOID ARTHRITIS
A DOUBLE BLINDFOLD TRIAL OF TREATMENT FOR ONE YEAR

BY

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Since the preliminary report on the use of mepacrine in the treatment of rheumatoid arthritis (Freedman and Bach, 1952), there has been a gradual appreciation of the value of 4-amino quinolone compounds for this condition. Many papers have appeared (Forestier and Certonciny, 1954; Scherbel, Schuchter, and Harrison, 1957; Erlendsson, 1958; Fuld and Horwich, 1958), but controlled trials have been few. The first (Freedman, 1956) dealt with 66 patients each observed for a period of 16 weeks. The finding that the chloroquine-treated patients did better than the controls was confirmed by trials undertaken by Rinehart, Rosenbaum, and Hopkins (1957), Cohen and Calkins (1958), and Kuipers (1959), in none of which was the period of comparison longer than 26 weeks. Bagnall (1957), convinced of the value of these drugs, abandoned his intention to conduct a controlled trial and published his findings of 4 years' treatment of patients, the longest series yet reported. With one equivocal exception (La Tona and Norcross, 1959), there has been widespread approbation by all authors for these compounds. The present report deals with observations in a double blindfold trial begun in 1956 in a group of patients each of whom was treated for a period of one year.

Method

Subjects.—Patients were drawn from those attending the Department of Physical Medicine at the London Hospital, those under the care of one of us at Hackney Hospital, and those from the Department of Physical Medicine at Chase Farm Hospital, Enfield.

Diagnostic Criteria.—Patients with rheumatoid type of arthritis with active inflammation of at least four joints and a raised erythrocyte sedimentation rate were admitted irrespective of the duration of the disease or the result of the sheep-cell agglutination test. These patients all satisfied the criteria as having definite rheumatoid arthritis according to the classification of the American Rheumatism Association (Ropes, Bennett, Cobb, Jacox, and Jessar, 1957).

Patients ill enough to be admitted to hospital were not accepted into the trial, and anyone within the trial was withdrawn if the condition so deteriorated as to warrant admission to hospital.

Treatment.—During the trial period all patients received eight 5-gr. tablets of enteric-coated aspirin daily, and if they were anaemic oral iron was also prescribed. The patients also received either chloroquine or dummy tablets of identical appearance, the physician not knowing which kind the patient was having throughout the trial. These tablets were prescribed according to the serial number given to the patient as each was admitted into the trial. A list of these numbers divided randomly into two groups, P and Q, was held by the pharmacist, who dispensed either P or Q tablets according to the serial number. The dispenser did not know which was the active preparation. Those patients who were receiving the active preparation were in fact taking chloroquine sulphate 200 mg. twice daily. In a few cases in both groups side-effects occurred; these were considered to be toxic effects and a reduction of dosage to one and a half tablets daily was made. Appropriate splinting and physiotherapy were also prescribed.

Assessment.—The patients were examined by one of us at a special clinic held for this purpose on a separate afternoon. At each visit they were asked specific questions concerning their symptoms and their need for analgesics other than those routinely prescribed, and about any change in their self-care and ability to work.

Special note was made of their colour, and the presence of oedema, nodules, lymph-glands, and rashes. The temporo-mandibular, clavicular, and manubrial joints and the spine as well as the limb joints were separately examined.

Joint tenderness was graded I, II, or III (I representing tenderness, II wincing, and III withdrawal of the affected

part). The sum of these tenderness figures was then recorded as total tenderness.

Strength of grip was measured on a mercury sphygmomanometer by the patient exerting as much pressure as possible on the folded cuff distended to a pressure of 30 mm. Hg. The mean of the pressures for the grip of the right and left hands was recorded as the strength of grip.

The time taken to walk 25 yards was recorded as the walking-time.

The dexterity of the hands was measured by recording the time taken to insert a lace in and out of the holes on one side of a boot.

The patients were assessed at intervals of 2 to 6 weeks. At each visit they were weighed and blood was taken for haemoglobin and erythrocyte sedimentation rate tests.

Blood for sheep-cell agglutination tests was taken at the beginning and the end of the year, as were *x*-rays of the hands and feet.

At the end of the trial these records provided figures expressing the degree of joint inflammation and joint function, and data from which subjective and objective clinical assessments could be made.

Material

There were 53 patients in the chloroquine group and 54 in the control group entering the trial. The ages and sex distribution (Table I) were similar in both groups, but Table II shows that the chloroquine group happened to contain an excess of patients with disease of less than one year's duration (ten against five) and a deficiency of those with more than 5 years' duration (thirteen against twenty).

Withdrawals

Three patients, subsequently ascertained as belonging to the control group, deteriorated so much that they had to be taken out of the trial.

One patient on chloroquine informed us that he was not attending further as he was fully recovered.

"Toxic" effects were sufficiently severe to cause four control cases and five chloroquine cases to discontinue treatment.

For various reasons including those mentioned above (Table III, opposite), altogether fourteen controls and eleven chloroquine patients did not complete the trial. There remained for comparison 42 patients in the chloroquine group and forty patients in the control group. Table II shows an excess of patients in the chloroquine group who had disease of less than one year's duration (nine as against four).

TABLE II

DURATION OF DISEASE (YEARS) AT ENTRY AND ON COMPLETION OF TRIAL

Series of Patients		At Entry		On Completion	
Therapy		Control	Chloroquine	Control	Chloroquine
Duration of Disease (yrs)	Less than 1	5	10	4	9
	1–4	29	30	21	22
	5–9	10	8	9	6
	10+	10	5	6	5
Total No. of Patients.. ..		54	53	40	42

Results

Joint Tenderness (Table IV, opposite).—Only three patients were entirely free of joint tenderness at the end of the year and all had received chloroquine. Thirteen of the control patients had widespread tenderness at the end of the year, whereas only four chloroquine patients had similar lack of improvement. The average figures for total tenderness were 28·4 in the control group and 27·0 in the chloroquine group falling to 25·4 and 13·5 respectively by the end of the year. The degree of improvement in the chloroquine group was statistically significant ($t = 5{\cdot}91$; $p < 0{\cdot}001$).

TABLE I

AGE AND SEX DISTRIBUTION AT ENTRY AND ON COMPLETION OF TRIAL

Series of Patients		At Entry						On Completion					
Therapy		Control			Chloroquine			Control			Chloroquine		
Sex		Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total
Age Group (yrs)	–39	1	6	7	0	8	8	1	5	6	0	7	7
	40–49	4	15	19	3	12	15	4	12	16	2	11	13
	50–59	5	14	19	6	15	21	4	9	13	5	10	15
	60–	3	6	9	1	8	9	2	3	5	0	7	7
	All Ages	13	41	54	10	43	53	11	29	40	7	35	42

TABLE III

REASONS FOR WITHDRAWALS FROM TRIAL

Therapy		Control		Chloroquine	
Reason	Deterioration	3	Severely ill at 17 weeks Severely ill at 39 weeks Worse at 15 weeks		None
	Toxic Effects	4	Giddiness; gastric upset Sore tongue Rash Paranoia	5	Unwell; nausea Light sensitivity; complete remission Unwell; wished to lie down Rash; deterioration; dosage interrupted Gastro-intestinal symptoms
	Intercurrent Illness	2	Disseminated lupus erythematosus Died; cerebral tumour	2	Died; carcinomatosis Pneumonia; treatment discontinued and not resumed
	Removal from District	0	None	1	Removal
	Failed to Attend	5	Defaulted after E.M.G. (2 cases) Worse; went to another hospital Thought she was getting worse No reason obtained	3	Because he was doing so well Sent letter at 14 weeks saying he wished to stop treatment Insisted on returning to phenylbutazone at 4 weeks
	Total	14		11	

TABLE IV

NUMBER OF PATIENTS WITH GIVEN TENDERNESS AT END OF COURSE OF TREATMENT RELATED TO INITIAL RANGE OF TENDERNESS

Range of Initial Tenderness	Therapy	No. of Patients	Range of Joint Tenderness at End of Course				
			0	1–10	11–20	21–30	31+
1–10	Control	2	—	—	—	2	—
	Chloroquine	3	1	2	—	—	—
11–20	Control	13	—	3	8	2	—
	Chloroquine	11	0	6	4	1	—
21–30	Control	13	—	1	8	1	3
	Chloroquine	13	1	6	5	0	1
31+	Control	12	—	—	2	—	10
	Chloroquine	15	1	5	4	2	3
Total	Control	40	—	4	18	5	13
	Chloroquine	42	3	19	13	3	4

Function Tests

Strength of Grip (Table V).—The mean strength of grip of the forty controls at the start of treatment was 125 mm. Hg, rising to 128 mm. Hg at the end of one year. The figures for the chloroquine group were 124 mm. Hg, rising to 165 mm. Hg. The improvement in those receiving chloroquine was statistically significant ($t = 3{\cdot}915$; $p < 0{\cdot}001$).

Dexterity (Table VI).—Both groups showed an improvement that was statistically significant (controls $t = 3{\cdot}2535$; $p < 0{\cdot}01$. Chloroquine $t = 4{\cdot}06$; $p < 0{\cdot}001$).

Walking Time (Table VI).—Here only the chloroquine group showed statistically significant improvement ($t = 3{\cdot}0001$; $p < 0{\cdot}01$).

Tenderness and Function Score.—This was obtained by awarding:

50 marks if there was no tenderness, *i.e.* $\left(\frac{100\text{-}0}{2}\right)$,

25 if the grip was 200 mm. Hg or more, *i.e.* $\left(\frac{200}{8}\right)$,

25 if the walking time was 20 sec., *i.e.* $\left(\frac{70\text{-}20}{2}\right)$,

making a possible total of 100.

TABLE V

CHANGE IN STRENGTH OF GRIP (mm. Hg) BETWEEN BEGINNING AND END OF TREATMENT

Therapy	No. of Patients	Improved		No Change (+ or − 10 mm. Hg)	Deteriorated	
		by 51 mm. Hg or More	by 11–50 mm. Hg		by 11–50 mm. Hg	by 51 mm. Hg or More
Control	40	5	10	9	15	1
Chloroquine	42	15	16	5	5	1

TABLE VI

DEXTERITY, WALKING, HAEMOGLOBIN, AND ERYTHROCYTE SEDIMENTATION RATE

Investigation	Therapy	Number of Patients	Average	
			Week 0	Week 52
a) Time for Lacing One Side of a Boot (sec.)	Control	40	49·1	41·1*
	Chloroquine	42	50·3	42·3*
b) Time for Walking 25 yds (sec.)	Control	40	26·9	25·1
	Chloroquine	42	24·1	21·8*
Hb (per cent.)	Control	40	82·4	80·6
	Chloroquine	42	80·5	82·1
Erythrocyte Sedimentation Rate (mm./hr Westergren)	Control	40	37·9	35·1
	Chloroquine	42	36·2	26·1*

* Improvement statistically significant

For example, if a patient had a total tenderness of 24, a grip of 160 mm. Hg, and a walking time of 40 sec., he was awarded $\frac{100\text{-}24}{2} + \frac{160}{8} + \frac{70\text{-}40}{2}$, *i.e.* a score of 73. The Figure (below) compares the scores at the beginning and end of the year for the control and chloroquine groups. The mean change for the control group was +2·1, while for the chloroquine group it was +12·2, which is statistically significant ($t = 6{\cdot}987$; $p < 0{\cdot}001$).

Haemoglobin Levels (Table VI).—There was no significant change in either group.

Erythrocyte Sedimentation Rate (Table VI).—Only the chloroquine group showed a significant improvement during the year, an average fall of 10·1 mm./hr (Westergren) ($t = 3{\cdot}771$; $p < 0{\cdot}001$).

Radiological Changes (Table VII).—The *x* rays of the hands and feet at the start and at the end of the

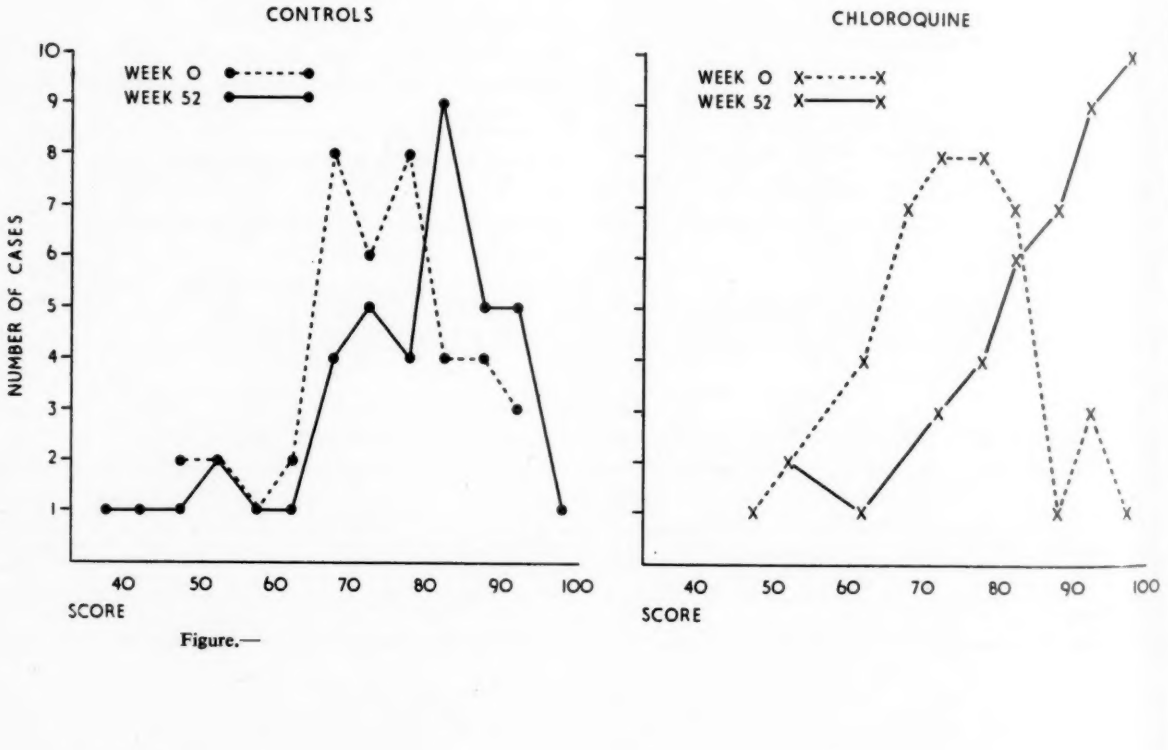

Figure.—

TABLE VII

RADIOLOGICAL CHANGES IN FILMS OF HANDS AND FEET AT BEGINNING AND END OF ONE YEAR'S TREATMENT

Therapy	No. of Patients	Time of Assessment	Grade						Change		
			0	1	2	3	4	Not Done	Worse	No Change	Better
Control	40	Week 0	3	1	16	10	9	1	12	27	0
		Week 52	1	1	11	16	11	—			
Chloroquine	42	Week 0	5	3	20	9	4	1	5	31	2
		Week 52	2	1	17	15	4	3			

trial were brought together and read by a single observer who had no knowledge of type of treatment given. The gradings were based on the incidence of articular erosions, joint narrowing, and subluxation.

Grade	Abnormality
0	none
1	doubtful
2	slight
3	moderate
4	severe

Changes within any particular grade were also recorded, although they might not be sufficient to alter the grading for severity. Improvement with regard to healing of erosions was observed in two chloroquine cases. Undoubted deterioration occurred in twelve of the control cases and five of the chloroquine cases.

Haemagglutination Tests (Table VIII).—Unfortunately, during the period of the trial, the method for carrying out diagnostic agglutination tests for rheumatoid arthritis was undergoing change. The Rose-Waaler sheep-cell agglutination test, the Ball modification of this test, and the Latex-fixation test were used successively and the tests were carried out not at one centre but at the three hospitals which the patients were attending. Table VIII merely summarizes the positive and negative results for what they are worth. The distribution of positive and negative cases was the same in both groups at the beginning of the trial, but at the end of the year the positive cases in the chloroquine group had fallen from 23 to 19, whereas in the control group they had increased from 23 to 32. One-third of all the cases at the beginning of the trial showed negative tests; at the end of the year almost half of the chloroquine cases and only one-fifth of the control cases were negative.

TABLE VIII

RESULTS OF HAEMAGGLUTINATION TESTS IN PATIENTS WHO COMPLETED COURSE

Therapy	Result of Test	No. of Cases	
		Week 0	Week 52
Control	Positive ..	23	32
	Negative ..	13	8
	Not done ..	4	0
	Total ..	40	40
Chloroquine	Positive ..	23	19
	Negative ..	13	22
	Not done ..	6	1
	Total ..	42	42

Functional Capacity* and Disease Activity† (Table IX, overleaf).—The gradings were those adopted by Duthie, Thompson, Weir, and Fletcher (1955):

* Grade I = Fit for all normal activities
Grade II = Moderate restriction.
Grade III = Marked restriction.
Grade IV = Confined to chair or bed (such cases were excluded from entry to the trial or withdrawn if they deteriorated to this grade).

† Grade 1 = Very Active (E.S.R. over 60 mm./hr, haemoglobin < 65 per cent., widespread inflammation).
Grade 2 = Moderately Active (E.S.R. 20 to 60 mm./hr, haemoglobin 65–85 per cent. several joints involved).
Grade 3 = Inactive (E.S.R. < 20 mm./hr, haemoglobin 85 per cent. or over, no joint inflammation).

Of all the indices for comparison which we have employed, functional capacity was the only one where there was a significant difference between the control and chloroquine cases, both those who entered the trial and those who remained after discounting withdrawals. This dissimilarity is probably attributable to the longer duration of the disease in the control cases. Functional capacity is dependent on structural change which cannot improve and disease activity which can. With respect to disease activity the two groups were comparable. As shown in Table IX, both in functional capacity and disease activity the chloroquine group made undoubted improvement.

TABLE IX

FUNCTIONAL CAPACITY AND DISEASE ACTIVITY AT BEGINNING AND END OF ONE YEAR'S TREATMENT

Grade		Control		Chloroquine	
		Week 0	Week 52	Week 0	Week 52
* Functional Capacity	I	12	16	15	27
	II	12	14	21	11
	III	16	10	6	4
	Total ..	40	40	42	42
† Disease Activity	1	1	2	2	2
	2	39	36	40	28
	3	0	2	0	12
	Total ..	40	40	42	42

Assessment of Response to Treatment (Table X).—At the end of the trial all the records were reviewed. On the basis of the patient's own replies it was possible to give an assessment of his own view of his improvement or deterioration, while the clinical and laboratory data permitted an objective assessment. Table X shows that about 50 per cent. of the control group thought they had improved but the objective impression was 30 per cent., and definite deterioration had occurred in 25 per cent. On the other hand, of those who received and tolerated chloroquine, 90 per cent. felt that they had improved, and 80 per cent. showed objective improvement, 15 per cent. having had a complete remission. Deterioration occurred in only 5 per cent. of the chloroquine cases.

Toxic Effects.—The side-effects of prolonged chloroquine administration at this dosage include blurred vision, giddiness, nausea, vomiting, diarrhoea, headache, pruritus, and a patchy dry dermatitis. Complaints of this nature were made by patients in both groups and were regarded as toxic effects. 33 out of the 53 patients who started on chloroquine had some such complaint, seven of them having more than one complaint, and 22 of the 54 controls had so-called toxic effects, six of them having more than one complaint. The actual number of such toxic symptoms is shown in Table XI. They were regarded as serious enough to warrant withdrawal from the trial in four of the control group and five of the chloroquine group (Table III).

TABLE XI

INCIDENCE OF TOXIC EFFECTS IN ALL PATIENTS WHO EMBARKED ON THE TRIAL

Therapy		Control	Chloroquine
Disturbances	Vision	4	15
	Gastro-intestinal ..	11	9
	Skin	7	16
	Nervous system ..	13	9
	Other	1	3
	Total	36 in 22 patients	52 in 33 patients
Patients with no Toxic Effects ..		32 out of 54	20 out of 53
Withdrawals		4	5

Discussion

Comparability of Groups before and after Withdrawals.—The random distribution of cases succeeded in providing similarity of both groups with regard to age and sex distribution, but not for duration of disease as there were five control cases and ten chloroquine cases with duration of disease of less than one year. The Table indicates that this difference still remained in those who completed the trial. Since such patients are known to do well without treatment, a separate analysis was undertaken of cases with more than 1 year's duration of arthritis. This showed results similar to those of the groups as a whole.

Results.—If one accepts the groups as comparable then the results are favourable to chloroquine.

TABLE X

SUBJECTIVE AND OBJECTIVE IMPRESSIONS OF RESPONSE TO TREATMENT

Impression	Therapy	Number of Patients	Grade of Response to Treatment						
			Improved			No Change	Worse		
			Much	Moderately	Slightly		Slightly	Moderately	Much
Subjective	Control	40	1	11	8	11	9	0	0
	Chloroquine	42	12	18	8	1	1	2	0
Objective	Control	40	1	7	6	14	10	2	0
	Chloroquine	42	7*	20	6	7	0	2	0

* Complete remission.

Though a few patients showed little or no response, most of the chloroquine group undoubtedly enjoyed a lessening of joint inflammation and improvement in function. The tests used to demonstrate this did, it must be admitted, depend on the examiner's assessment and the co-operation of the patient. However, the erythrocyte sedimentation rate was an entirely objective estimation and this too showed a significant improvement in the chloroquine group. The changes in technique in the haemagglutination tests were unfortunate, but we feel that the results should not be dismissed, first because these changes would have affected both groups equally, and secondly because the changes of method made the tests more sensitive, so that more positive results would be detected at the final examination. Confirmation of this very favourable response to chloroquine is of some importance, since it contrasts with the increase in haemagglutination titres that occurred in patients receiving prednisone (Medical Research Council and Nuffield Foundation, 1959).

The differences observed in the progression of *x*-ray changes in the two groups should not perhaps be used as an argument in favour of chloroquine. A longer period of observation and a more detailed assessment of individual joints should be undertaken to provide a system of scoring for use by the statistician.

Safety of Chloroquine.—Side-effects of various kinds occurred in 33 cases (62·5 per cent.), but the fact that similar symptoms also occurred in 22 (40 per cent.) of the control cases shows that it should not be assumed that the drug is alone responsible. A small reduction in dosage may enable the patient to tolerate the drug and yet have worthwhile benefit. In this investigation, with a maximum dosage of 400 mg. chloroquine sulphate daily for one year, no irreversible toxic effect occurred. Experience outside this trial (Hobbs, Sorsby, and Freedman, 1959), however, has revealed one serious side-effect, a retinopathy occurring in a few patients who had received more than 2 years of continuous treatment with this group of drugs. It may therefore be advisable to limit the period of treatment to 2 years.

Summary

A double blindfold trial is reported in which patients with rheumatoid arthritis received either chloroquine or dummy tablets. 107 patients entered the trial at the three centres which participated; 53 received the drug and 54 the placebo. The dose of chloroquine sulphate was 400 mg. daily. All patients also recieved 40 gr. aspirin daily and appropriate physiotherapy.

There were 25 withdrawals from the trial for various reasons, fourteen control cases and eleven chloroquine cases. Toxic effects were responsible for five withdrawals in the chloroquine group and four in the control group. Three of the control cases so deteriorated that they had to be withdrawn from the trial.

There remained forty patients in the control group and 42 in the chloroquine group who completed 1 year of treatment.

The patients who received and tolerated the chloroquine showed statistically significant improvement with respect to indices of clinical assessment and erythrocyte sedimentation rate. No change was observed in the average haemoglobin estimations. Haemagglutination tests were done by different methods over the period of the trial, but the changes noted indicated marked improvement in the chloroquine group. The *x*-ray changes were not submitted to statistical analysis but tended to show less progression in the chloroquine group than in the control group.

Definite general improvement occurred in 30 per cent. of the forty controls and 80 per cent. of the 42 patients on chloroquine who completed the year of treatment. Excluding defaulters, substantial improvement occurred in 60 per cent. of the patients who began treatment with chloroquine. Deterioration occurred in 25 per cent. of the control cases, and in only 5 per cent. of the chloroquine cases. Chloroquine sulphate in this dosage given for one year proved to be perfectly safe.

We wish to thank Dr. W. S. Tegner who kindly allowed us to treat his patients at a Special Clinic at the London Hospital and for his comments on this paper. Our thanks are also due to Dr. R. M. Mason for allowing us to treat some of his patients at Chase Farm Hospital, Enfield. We also thank Miss G. Orme of the Department of Physical Medicine, at the London Hospital, Mrs. Yandell at Chase Farm Hospital, and Sister I. Rowatt at Hackney Hospital for their help in running the Special Clinics.

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Chloroquine dans l'arthrite rhumatismale.—Un essai à "double feinte" de traitement pendant un an

RÉSUMÉ

On décrit les résultats d'un essai à "double feinte" (*double blind*) où les malades atteints d'arthrite rhumatismale recevaient des comprimés soit de chloroquine, soit d'une substance inerte. On commença l'essai dans trois centres hospitaliers sur un total de 107 malades; 53 d'entre eux recevaient de la chloroquine et 54 la substance inerte. La dose de sulfate de chloroquine fut de 400 mg. par jour. En même temps, tous les malades recevaient à peu près 2,7 g. d'aspirine par jour et toute physiothérapie nécessaire.

Pour des raisons diverses on retira de l'essai 25 malades dont 14 du groupe témoin et 11 du groupe traité. Des effets secondaires furent responsables de 5 cas retirés du groupe traité et de 4 cas du groupe témoin. Trois cas dans le groupe témoin subirent une telle détérioration, qu'on était obligé de les retirer de l'essai.

Pour compléter l'année expérimentale il resta donc 40 malades dans le groupe témoin et 42 dans le groupe traité par la chloroquine.

Les malades qui reçurent et tolérèrent la chloroquine accusèrent une amélioration statistiquement significative en ce qui concerne les indices d'évaluation clinique et la vitesse de sédimentation globulaire. Le taux moyen d'hémoglobine demeura sans changer. Des réactions d'hémagglutination furent effectuées par de différentes méthodes pendant la période d essai, mais les changements notés indiquèrent une amélioration nette chez des malades du groupe traité par la chloroquine. Les résultats radiologiques ne furent pas soumis à l'analyse statistique, mais ils tendaient à montrer moins de déterioration dans la groupe traité.

Une amélioration générale définie survint dans 30 pour cent des 40 malades du groupe témoin et dans 80 pour cent des 42 malades qui avaient accompli un an de traitement par la chloroquine. Une aggravation de la symptomatologie fut observée en 25 pour cent des témoins et seulement en 5 pour cent des traités. Le sulfate de chloroquine à la dose administrée pendant un an s'avéra parfaitement sûr.

Cloroquina en artritis reumatoide.—Ensayo a "doble disfraz" de tratamiento por un año

SUMARIO

Se describen los resultados de un ensayo a "doble disfraz" (*double blind*), en el que enfermos con artritis reumatoide recibieron unos cloroquina, otros pastillas inertes, apropiadamente disfrazadas. Entre los tres centros participantes en la prueba se reunieron 107 enfermos; 53 de ellos recibieron el medicamento y los otros 54 la substancia inerte. La dosis de sulfato de cloroquina fué 400 mg. diarios. Todos los enfermos recibieron al mismo tiempo aproximadamente 2,7 g. diarios de aspirina y la adecuada fisioterapia.

Fueron retirados de la investigación por diversas causas 25 enfermos, 14 entre el grupo de control y 11 entre él que tomaba cloroquina. Efectos tóxicos fueron responsables de cinco casos retirados en el grupo tratado con cloroquina y de cuatro casos en él de control. Tres de los casos del grupo de control se agravaron tanto, que tuvieron que ser retirados de la investigación.

Quedaron, por tanto, 40 enfermos en el grupo de control y 42 en el grupo tratado con cloroquina, durante un año.

Los enfermos que recibieron y toleraron la cloroquina presentaron una mejoría estadísticamente significativa con respecto a los indicios de valoración clínica y velocidad de sedimentación eritrocitaria. No se apreció cambio alguno en el termino medio de la cifra de hemoglobina. Reacciones de hemaglutinación se llevaron a cabo por diferentes métodos durante el período de investigación; los cambios observados indicaron una clara mejoría en los pacientes del grupo que recibió cloroquina. Los datos radiológicos no fueron sometidos a anáisis estadístico, pero tendían a mostrar una progresión más lenta en el grupo tratado que en el grupo de control.

Mejoría general definida se presentó en el 30 por ciento de los 40 enfermos de control y en el 80 por ciento de los 42 que completaron un año de tratamiento con cloroquina. Una agravación de la sintomatología se observó en el 25 por ciento del grupo de control y solamente en el 5 por ciento del grupo en tratamiento. El sulfato de cloroquina a la dosis administrada, durante un año, demostró ser perfectamente seguro.

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CLINICAL TRIAL OF THE THERAPEUTIC VALUE OF CERTAIN ANTIRHEUMATIC DRUGS

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In addition to the so-called basic therapy employed in the treatment of rheumatoid arthritis, a number of drugs are in general use. Many years of experience have shown the value of aspirin, aminopyrin (pyramidon), phenylbutazone (butazolidin), and gold. This evaluation is based primarily on estimates of their antirheumatic and analgesic effects, as well as on considerations of the risk of toxicity.

It is not proposed to discuss the possibility of a distinct differentiation between the analgesic and antirheumatic effects of these drugs on the one hand and the antirheumatic and antiphlogistic properties on the other. This subject has been fully treated by Winder (1959).

A better understanding of the course of rheumatoid arthritis treated exclusively with basic therapy has established that, because of the variable and unpredictable course of the disease, any evaluation of antirheumatic drugs must satisfy a number of demands. Such an evaluation can be carried out most successfully, by methods which have been worked out largely by British investigators, in so-called "double-blind" trials, by which neither the patient nor the investigator knows which drug is being administered.

A double-blind test with salicylamide and a placebo has been reported by Batterman and Grossman (1955), but no similar study of the value of aminopyrin has come to the authors' attention. Five blind investigations of phenylbutazone have been reported (Steinbrocker, Berkowitz, Carp, Ehrlich, and Elkind, 1951; Ansell, Fearnley, Bywaters, and Meanock, 1953; Fjellström, Goldberg, Lindgren, and Nilsson, 1957; Smyth and Clark, 1957; Vaughn, Howell, and Kiem, 1959). The method used by Hajnal, Sharp, and Popert (1959), who tested aspirin, prednisone, and phenylbutazone, is not comparable with the usual double-blind type of trial.

Our object was not only to assess the clinical value of aspirin, aminopyrin, and phenylbutazone in relation to a placebo, but at the same time to compare these drugs with each other as regards therapeutic activity and toxicity.

Method

Material.—191 patients from the Clinical Centres for Rheumatic Diseases N and S (Rotterdam) with "definite rheumatoid arthritis" (A.R.A. criteria: Ropes, 1959) received, in addition to the basic treatment, a 6-week course of drugs in the form of powders. The choice of the first powder to be administered was determined by a random list, as was the order in which the drugs and the placebo were taken by the patient.

Disease Activity.—This was measured before and after the course of treatment according to four criteria:

(1) Strength of grip (mm. Hg), measured by a standardized technique (average for both hands).

(2) Pain on firm digital pressure over the affected joint (mostly the metacarpophalangeal), measured in four grades:

0 = No pain
1 = Slight pain
2 = Severe pain (with wincing)
3 = Pain (with wincing and withdrawal)

(3) Erythrocyte sedimentation rate (mm./hr, Westergren).

(4) Patient's subjective opinion as to his condition at the end of the 6 weeks, using the following ratings:

0 = Unchanged
−1 = Worse
−2 = Much worse
+1 = Somewhat improved
+2 = Greatly improved

Grouping the Patients.—The three drugs and the placebo were identified by the numbers I, II, III, IV, and they were handled under these designations throughout the experiment, the names not being disclosed even to the authors until the end of the trial.

TABLE I

GROUPING OF 191 PATIENTS AND CLINICAL PARTICULARS AT START OF COURSE

Drug No.	Completed Course	Sex		Mean Age (yrs)	Mean Duration (yrs)	Mean* Functional Capacity	Mean E.S.R. (mm./hr, Westergren)	Mean Grip (mm. Hg)	Mean* Pain on Pressure
		Male	Female						
I	Yes	23	38	50·9	8·0	1·8	23·1	149	1·43
	No	10	19	52·1	7·5	1·9	23·8	184	1·45
	Total ..	33	57	51·2	7·9	1·8	23·3	160	1·44
II	Yes	24	40	53·9	6·3	1·8	27·9	149	1·46
	No	10	23	50·7	8·0	1·9	22·7	162	1·53
	Total ..	34	63	52·8	6·9	1·8	26·1	154	1·48
III	Yes	30	41	51·3	6·2	1·8	23·2	157	1·48
	No	13	33	53·5	7·2	1·8	26·4	151	1·47
	Total ..	43	74	52·2	6·6	1·8	24·5	155	1·48
IV	Yes	23	34	52·0	6·7	1·9	26·1	148	1·61
	No	10	33	52·7	5·9	1·7	22·8	150	1·48
	Total ..	33	67	52·3	6·3	1·8	24·7	149	1·55
Total Patients		73	118						

* Mean: This term is not justifiable statistically, but convenient as an index in summarizing the data.

The 191 patients were grouped according to the number of the first drug used. The clinical details as at the start of the experiment are shown in Table I.

Dosage.—The following dosages were used:

Phenylbutazone, three daily doses of 200 mg.;
Aminopyrin, 500 mg., three times daily;
Aspirin, 1 g., three times daily (at the start of our trial it was not sufficiently known that the dose should have been at least 6 g. to be compared with 600 mg. phenylbutazone);
Sach. lact., 1 g., three times daily.

The powders were all given the same bitter taste by the addition of a small amount of quinine.

2 weeks after the conclusion of one course of powders the next drug in the series was administered for a further 6 weeks. In this way it was possible to compare the effect of various drugs on various patients, and all also received the basic treatment throughout the investigation.

Toxicity.—When toxic symptoms appeared, an attempt was made to carry on with a smaller dosage, but the administration was discontinued if toxic signs persisted, and a few patients defaulted.

In connexion with the danger of intoxication, all patients were checked weekly during the consulting hour as to their subjective complaints. Weekly procedures included a leucocyte count, and the urine was checked for albumen, urobilin and sediment.

Results

Table II shows the percentage of patients who completed courses of each drug. The chances of completing the course decreased in the sequence I-II-III-IV; in other words, Drug IV seems to have been more toxic than Drug I; the differences in frequency of completion, however, are not significant.

TABLE II

PERCENTAGE OF PATIENTS WHO COMPLETED THE COURSES OF EACH DRUG

Drug No.		I	II	III	IV
Six-week Course Completed		68	66	61	57
Course Discontinued	After Consulting Doctor ..	18	25	27	35
	Without Consulting Doctor	14	9	12	8
Total	Percentage	100	100	100	100
	Number of Subjects ..	90	97	117	100

Table III (opposite) shows the reasons for discontinuing courses. The most important toxic reactions were the following:

(1) *Decrease in the Number of Leucocytes* (lower than 4,000/c.mm.).
Drug II—0
Drugs I and III—5 each
Drug IV—6.

(2) *Oedema.*
Drug IV—6.

(3) *Stomach Complaints.*
Drug II—16
Drug III—13
Drug IV—8
Drug I—5

The numbers of separate complaints are too small for the differences to be significant.

TABLE III

REASONS FOR DISCONTINUING COURSES

Drug No.			I	II	III	IV
Toxic Effects	Itching		3	1	5	4
	Decrease in Number of Leucocytes (below 4,000)		5	—	5	6
	Stomach Complaints		5	16	13	8
	Throat Complaints		1	3	3	1
	Gastro-Intestinal Bleeding		—	1	—	—
	Dizziness		—	—	2	—
	Exanthema		2	1	3	5
	Abdominal Complaints		—	1	—	1
	Ringing in the Ears		—	—	—	2
	Thrombophlebitis		—	1	—	—
	Stomatitis		—	—	—	1
	Icterus		—	—	—	1
	Oedema		—	—	—	6
	Headache		—	—	1	—
	Total	No.	16	23	32	35
		Per cent.	17	24	27	35
Patients Defaulted			13	9	14	8
Total Discontinued		No.	29	33	46	43
		Per cent.	32	34	39	43

It is also possible, since so many of the complaints were subjective in nature, that they came from patients who invariably complained; and indeed the percentage of persons who discontinued the experiment of their own accord (*i.e.* not on the advice of their physician) decreased with the number of courses taken: 49 per cent. having taken one course, 45 per cent. two courses, 32 per cent. three courses, and 28 per cent. four courses. This suggests the operation of a certain psychological factor.

There was no indication that the frequency of discontinuation depended on the drug with which the series was begun.

Table IV gives the means of the results obtained by evaluating the courses of each drug separately. Table I shows that the four groups to which patients were allotted at random agreed well as to age, sex, duration of disease, functional capacity, erythrocyte sedimentation rate, grip, and pain on pressure. It must therefore be concluded that the difference in the results was caused by differences in the effects of the drugs.

As not all persons received a complete course with each of the four drugs it was deemed necessary to compare also the effect of the drugs in pairs, using the results of only those persons who were treated with both; these comparisons were made separately for grip, pressure pain, erythrocyte sedimentation rate, and subjective evaluation. These detailed comparisons were made as follows:

Drugs	No. of Patients
I and II	34
I and III	28
I and IV	17
II and III	36
II and IV	19
III and IV	27

In Table V (overleaf) the result of each comparison is given by an arrow. The points of the arrows indicate the best results. A double arrow is used when the difference is significant at the 5 per cent. level. Below the diagram the drugs are shown in order of effectiveness.

Table VI (overleaf) compares both sequences, namely that obtained by mutual comparison (Table V) and that obtained by evaluating the courses of each drug separately (collective average, see Table IV).

Grip.—The sequence in both Tables is I, III, II, IV.

Pain.—There is agreement for I and III and disagreement for II and IV.

Erythrocyte Sedimentation Rate.—There is no agreement at all.

Subjective Improvement.—Complete agreement is seen in the sequence I, II, III, and IV, in the sense that IV is significantly higher than the rest.

TABLE IV

COURSES EVALUATED SEPARATELY

Criterion of Assessment		Drugs in Order of Effectiveness			
Strength of Grip	Drug	I	III	II	IV
	Average	−2·5	1·1	3·5	24·2*
	No.	61	71	64	57
E.S.R.	Drug	IV	I	III	II
	Average	0·5	0·4	−2·0	−3·7†
	No.	57	61	71	64
Pain on Pressure	Drug	I	III	II	IV
	Average	−0·1	−0·2†	−0·2*	−0·5*
	No.	61	71	64	57
Subjective Evaluation	Drug	I	II	III	IV
	Average	0·2*	0·3*	0·4*	0·6*
	No.	61	64	71	57

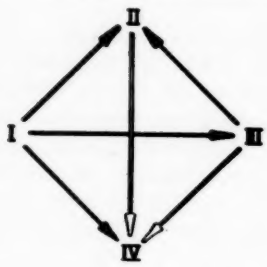
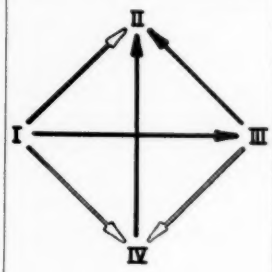
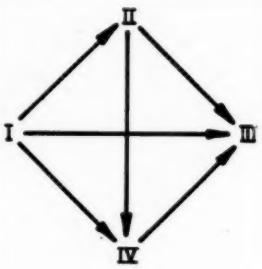
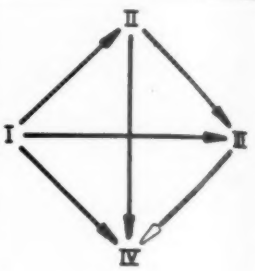
* Significant at the 1 per cent. level.
† Significant at the 5 per cent. level.

Discussion

There is therefore some disagreement between the sequence found by comparing the drugs in pairs and that found by comparing the means for all observations with each other. Nevertheless,

TABLE V

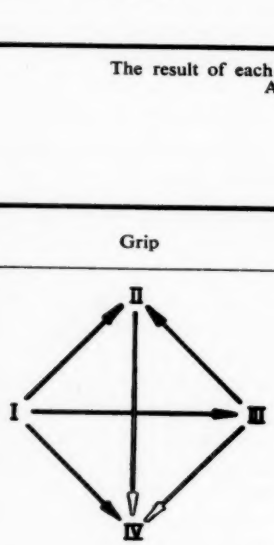
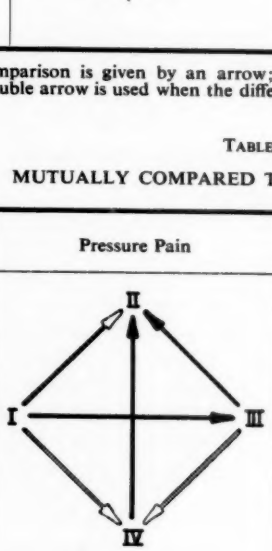
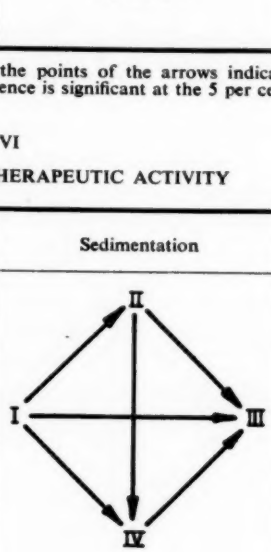
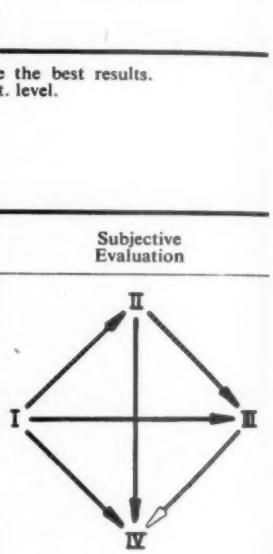
MUTUALLY COMPARED THERAPEUTIC ACTIVITY

Grip	Pressure Pain	Sedimentation	Subjective Evaluation
			
Sequence According to Diagram: I-III-II-IV	I-III-IV-II	I-II-IV-III	I-II-III-IV

The result of each comparison is given by an arrow; the points of the arrows indicate the best results. A double arrow is used when the difference is significant at the 5 per cent. level.

TABLE VI

MUTUALLY COMPARED THERAPEUTIC ACTIVITY

Grip	Pressure Pain	Sedimentation	Subjective Evaluation
			
Sequence According to Diagram: I-III-II-IV	I-III-IV-II	I-II-IV-III	I-II-III-IV
Sequence According to Collective Average: I-III-II-IV†	I-III*-II†-IV†	IV-I-III-II*	I†-II†-III†-IV†

* Significant at the 5 per cent. level.
† Significant at the 1 per cent. level.

in general, Drug I gives the least effect and Drug IV the most (excluding the erythrocyte sedimentation rate).

At this point the reader will be curious, as indeed were the authors, at the conclusion of the experiment and the statistical analysis, to know which number stood for which drug. The code was as follows:

I = Placebo
II = Aspirin
III = Aminopyrin (Pyramidon)
IV = Phenylbutazone.

Conclusion

The placebo as well as the drugs had, as was to be expected, a favourable effect on the symptoms of rheumatoid arthritis. This must be ascribed to the happily ever-present tendency to spontaneous recovery from rheumatoid arthritis, and also to the effect of suggestion which is inherent in all placebos.

Aspirin, aminopyrin, and phenylbutazone, however, had an appreciably better effect than the placebo, and of these phenylbutazone gave the best results. The authors wish to confine their conclusions from this experiment to the statement that, in this trial (bearing in mind the inadequacy and limitations of the quantitative criteria), phenylbutazone proved to be a better analgesic drug in cases of rheumatoid arthritis, than aminopyrin or aspirin in the dosages used.

The number of discontinued courses indicates that the administration of a placebo may be followed by the signs and symptoms of toxicity and intolerance (Table III). The clear-cut decrease in the number of leucocytes in patients taking the placebo must certainly have been due to a spontaneous fluctuation in the leucocyte count, but it led the authors, with exaggerated caution, to terminate the course.

The fact that toxicity increased in the sequence placebo, aspirin, aminopyrin, and phenylbutazone points to the conclusion that phenylbutazone is most likely to cause toxic reactions, although the differences were not large enough in these series to be significant.

Summary

In a "double-blind" trial of drugs in the treatment of rheumatoid arthritis, 191 patients with definite rheumatoid arthritis (American Rheumatism Association criteria) were given in four successive courses of 6 weeks: three daily doses of 1 g. aspirin, three daily doses of 0·5 g. aminopyrin, three daily doses of 200 mg. phenylbutazone, and three daily doses of a placebo.

All the powders looked the same and had the same taste. The order in which the drugs and the placebo were taken by the patient was determined by chance. Between each period of 6 weeks there was an interval of 2 weeks.

All the patients were examined at the beginning and end of each period by one of the authors and the improvement or deterioration was noted according to the following criteria:

(1) Hand grip (mm. Hg);
(2) Tenderness on pressure (metacarpophalangeal joints);
(3) Erythrocyte sedimentation rate (Westergren);
(4) Subjective judgment of the therapeutic result.

The results of this trial suggest that, in the dosages used, phenylbutazone is the best analgesic drug in rheumatoid arthritis, followed by aminopyrin and aspirin in that order, and the authors desire to limit their conclusions to this statement. Toxic reactions were least with the placebo, and increased with aspirin, aminopyrin, and phenylbutazone in that order, but the differences are not large enough to be significant in this series of patients.

The authors acknowledge with gratitude the co-operation of Dr. E. F. Drion and Mr. Th. J. D. Erlee of the Statistical Department of Toegepost Natuurkundig Onderzoek, The Hague, who did all the statistical work essential for this study, and gave much valuable criticism and advice.

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Essai en clinique de la valeur thérapeutique de certains médicaments antirhumatismaux

RÉSUMÉ

En un essai à "double feinte" (*double-blind*) de l'efficacité de certains médicaments dans le traitement de l'arthrite rhumatismale, 191 malades atteints de cette maladie (selon les critères de l'*American Rheumatism Association*) reçurent, en quatre cures successives de 6 semaines, trois fois par jour, une des substances suivantes: 1 g. d'aspirine, 0,5 g. d'aminopyrine, 200 mg. de phenylbutazone ou une poudre inerte.

L'aspect et la saveur de toutes les poudres était la même. L'ordre d'administration des médicaments et de la poudre inerte à chaque malade fut déterminé par hasard. Chaque période de 6 semaines fut séparée par 2 semaines sans traitement.

Tous les malades furent examinés au début et à la fin de chaque période de traitement par un des auteurs et l'amélioration ou la détérioration fut déterminée selon les critères suivants:

1. La force de la poigne (mm. de Hg)
2. Douleur à la pression (articulations métacarpophalangiennes)
3. Vitesse de sédimentation globulaire (Westergren)
4. Jugement subjectif du résultat thérapeutique.

Les résultats de cet essai indiquent que la phénylbutazone est le meilleur des analgésiques dans l'arthrite rhumatismale, suivi par l'aminopyrine et l'aspirine dans cet ordre, et les auteurs désirent limiter leurs conclusions à cela. En ce qui concerne les réactions toxiques, elles furent minimes avec la poudre inerte et augmentèrent avec l'aspirine, l'aminopyrine et la phénylbutazone dans cet ordre, bien que les différences ne soient pas suffisantes pour être significatives dans cette série de cas.

Prueba clinica sobre el valor terapéutico de ciertos medicamentos antirreumáticos

Sumario

En una prueba a "doble disfraz" (*double-blind*) de la efectividad de ciertos medicamentos en el tratamiento de la artritis reumatoide, 191 enfermos padeciendo de tal enfermedad (de acuerdo con los criterios de la *American Rheumatism Association*) recibieron, en cuatro períodos sucesivos de 6 semanas: 3 dosis diarias de 1 g. de aspirina, 3 dosis diarias de 0,5 g. de aminopirina, 3 dosis diarias de 200 mg. de fenilbutazona y 3 dosis diarias de un polvo inerto ("placebo").

Todos los medicamentos fueron administrados en forma de polvo y todos ellos eran iguales a la vista y tenían el mismo sabor. El orden en que los medicamentos y el "placebo" fueron administrados al paciente se determinó al azar. Entre cada período de 6 semanas de tratamiento se intercalaron 2 semanas de descanso.

Todos los enfermos fueron examinados al principio y al final de cada período de tratamiento por uno de los autores y la agravación o la mejoría se determinó con arreglo a los siguientes criterios:

1. Fuerza al asir con la mano (mm. de Hg)
2. Dolor provocado a la presión (articulaciones metacarpofalángeas)
3. Velocidad de sedimentación eritrocitaria (Westergren)
4. Juicio subjetivo del resultado terapéutico.

Los resultados de esta prueba sugieren que la fenilbutazona es el mejor de los analgésicos en la artritis reumatoide, seguida por la aminopirina y la aspirina en este orden, deseando los autores limitar sus conclusiones a la expresada. En cuanto a las reacciones tóxicas, fueron mínimas con el "placebo" y aumentaron con la aspirina, aminopirina y fenilbutazona en este orden aunque las diferencias no fueron suficientes par ser significativas en esta serie de casos.

Ann. rheum. Dis. (1960), **19**, 257.

INTRA-ARTICULAR THERAPY IN OSTEO-ARTHRITIS

COMPARISON OF HYDROCORTISONE ACETATE AND HYDROCORTISONE *TERTIARY*-BUTYLACETATE

BY

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The intra-articular injection of hydrocortisone acetate is commonly used in the treatment of osteo-arthritis, although its action in this disease has received less careful study than in rheumatoid arthritis. In 1955 a less soluble ester, hydrocortisone *tertiary*-butylacetate (TBA) was developed for intra-articular therapy with the claim that its effects were more pronounced and of longer duration (Hollander, Brown, Jessar, Udell, Smukler, and Bowie, 1955).

The purpose of the present trial was to evaluate both drugs in the treatment of osteo-arthritis by a double-blind, crossover method. Each patient received both compounds as well as placebo and thus served as his own control. This formed part of a wider study of the value of intra-articular therapy in rheumatic disease. The results of the present investigation will be compared with those obtained in rheumatoid arthritis (Chandler, Wright, and Hartfall, 1958).

Design of Trial

25 patients whose main complaint arose from osteo-arthritis of the knees were included in the trial. In thirteen both knees were treated, and in twelve only one knee, giving a total of 38 joints suitable for trial. No patient had received intra-articular therapy within 2 months of the start of the trial. Symptomatic treatment remained constant throughout the period of study which was conducted under out-patient conditions.

The trial consisted of three courses of treatment (hydrocortisone acetate, TBA, and placebo) each of four fortnightly injections, with 8 weeks rest between treatments. Dosages of TBA and hydrocortisone were 25 mg. in 1 ml. fluid. The placebo (1 ml.) was the vehicle used as the suspending and preserving agent for the active compounds. The order of courses in each patient was randomized from a master sheet in which names were entered consecutively.

The fortnightly assessments comprised the following measurements:

Walking time over 75 yards;
Range of joint movement and limitation of extension determined by a goniometer;
Tenderness (graded 0 = none, 1 = slight, 2 = definite, 3 = wincing, 4 = withdrawal and/or exclamation);
Pain (graded 0 = none, 1 = slight on walking, 2 = marked on walking, 3 = mild at rest, 4 = severe at rest).

Radiographs of the knees were obtained before and after the trial.

Results

Three patients failed to complete the trial; two defaulted after the second course of injections, and one developed an unrelated disease after the third injection of the second course. This resulted in five knees not receiving a course of placebo injections.

The specific data (walking time, etc.) derived from the first assessment in each treatment period were compared with the same measurements made at the four assessments in the succeeding 8-week rest period. Changes in walking time and joint movement were estimated as a percentage of the pre-treatment measurements; changes in limitation of extension were calculated as a percentage of maximal joint range (145°). Although pain and tenderness were graded at each assessment, because this parameter is entirely subjective, differences were calculated on the basis of improvement and no improvement. In this way the effect of treatment, both immediate and sustained, was calculated for each knee for each of the three treatments. The mean change for each of the three groups (hydrocortisone, TBA, and placebo) between pre-treatment assessments and each of the four post-treatment assessments was analysed by conventional statistical methods.

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Pain.—At the second week after the course of injections a greater proportion of the knees receiving hydrocortisone and TBA improved than did those receiving the placebo (Table I). The response to TBA was significantly better than that to the placebo ($P < 0{\cdot}02$), but the greater improvement following hydrocortisone when compared with placebo did not achieve the level of significance ($P < 0{\cdot}3$).

TABLE I
EFFECT ON PAIN OF HYDROCORTISONE, HYDROCORTISONE TBA, AND PLACEBO AT THE SECOND WEEK AFTER THE COURSE OF INJECTIONS

Result	Injection		
	Hydrocortisone	TBA	Placebo
Improvement	19	25	12
No improvement ..	19	13	21
Total Knees ..	38	38	33

There was no significant difference between the response to the two active drugs ($P < 0{\cdot}2$). At subsequent assessments there was no significant difference between the response to any of the injections.

Other Parameters.—No significant improvement in walking time, range of movement, limitation of extension, or tenderness was apparent after the injection of the two drugs compared with placebo.

Advantage of First Treatment

It has been suggested that, irrespective of the nature of the substance injected, the first course of injections given to a patient with rheumatoid arthritis will produce subjective improvement (Fearnley, Lackner, Meanock, and Bywaters, 1956). This possibility was therefore studied by comparing the improvement following the first course of injections with that following the second and third courses which were grouped together for purposes of analysis (Table II).

TABLE II
COMPARISON OF EFFECT OF FIRST COURSE OF INJECTIONS WITH EFFECT OF SUBSEQUENT COURSES

Mobility	Mean Improvement			
	First Course	Subsequent Course	Standard Error of Mean Difference	*P*
Walking Time (per cent. of patients)	9·5	1·1	±2·42	<0·01*
Range of Movement (per cent. of knees) ..	3·74	1·76	±1·17	<0·1
Limitation of Extension (per cent. of knees) ..	0·8	0·28	±0·86	<0·6

* Significant difference.

Only with walking time did the first course of treatment show a significant advantage over subsequent treatments. Here the difference was very striking. The mean improvement after the first course was 9 per cent. compared with 1 per cent. after subsequent courses. The difference is highly significant ($P < 0{\cdot}01$).

The improvement 2 weeks after the first injection of the first course was then compared with the improvement 2 weeks after the second injection of that course. There was no significant difference between the effect of the first and the second injection.

Complications

In two knees there was increased pain and stiffness lasting 2 and 3 days respectively after the injection of TBA. One patient complained of swelling of the ankle on two occasions after the injection of TBA, but no abnormality was seen at his next visit to the clinic.

Radiological Changes

Radiographs of each injected knee (antero-posterior and lateral) were taken at the beginning and end of the trial. The *x*-ray appearances were graded into four categories for osteo-arthritis (Kellgren and Lawrence, 1957):

1 = doubtful,
2 = minimal,
3 = moderate,
4 = severe.

In addition, the films were examined for evidence of osteoporosis and erosions. The initial films showed one knee with Grade 1 changes, nine with Grade 2, 21 with Grade 3, and seven with Grade 4. No deterioration in the osteo-arthritic lesions was seen during the period of the trial. Osteoporosis and erosions did not develop in any joint.

Discussion

Previous Reports.—Local injection into an involved joint has long been practised as a useful adjunct in the treatment of rheumatic diseases. It has many advantages, particularly in that systemic complications do not occur. Hollander, Brown, Jessar, and Brown (1951) first used hydrocortisone acetate for intra-articular injection, and the drug has since come to be generally regarded as beneficial in the treatment of rheumatoid arthritis and osteo-arthritis. However, controlled trials of its value have been few, and most reports have dealt with the authors' experience in retrospect. Moreover, in many reports, little distinction has

been made in analysis between the results in patients with rheumatoid arthritis and those in patients with osteo-arthritis (Hollander and others, 1951; Duff, 1956; Zuckner, Machek, and Ahern, 1956; Bonner, 1959). In a strictly controlled study (Chandler, Wright, and Hartfall, 1958), it was demonstrated that both hydrocortisone acetate and its *tertiary*-butylacetate derivative had a significant advantage over a placebo in the treatment of the knees of patients with rheumatoid arthritis. Improvement was generally greater and of longer duration with TBA than with hydrocortisone, but the difference was not significant.

Even greater value has been claimed for both these agents in osteo-arthritis (Hollander and others, 1951; Desmarais, 1952; Hollander and others, 1955; Zuckner, Machek, Caciolo, Ahern, and Ramsey, 1958). Williams (1958) claimed that TBA was effective over a longer period than hydrocortisone, but Kehr (1959) could detect no difference.

In the present study the response to treatment with respect to pain and tenderness has been classed as improved or not improved.

It was felt that to apply statistical methods to numbers assigned for grades of pain and tenderness would be merely to cover an edifice of inaccuracy with a coat of scientific paint. On these criteria the only significant improvement obtained from the active compounds was that in respect of pain; 2 weeks after the injection of both drugs less pain was experienced than after the placebo, and this was statistically significant ($P < 0{\cdot}02$) in the case of TBA. There was no significant difference between the active drugs. At the fourth and subsequent weeks after injection, however, neither drug conferred any significant advantage over the placebo. The effect of TBA although significant was transient. The fact that the improvement following hydrocortisone was not significant at the second week suggests that its effect is even more short lived than that of TBA.

The benefit derived from these drugs was therefore much less marked than that previously obtained under similar conditions in patients with rheumatoid arthritis who improved in all criteria of assessment for periods of 2 to 8 weeks. Nor do our findings accord with the majority experience (Hollander and others, 1951; Desmarais, 1952; Williams, 1958; Kehr, 1959); yet the results are not unexpected in view of the fundamentally different pathology of the two diseases. It is to be anticipated that the inflammatory arthritis of rheumatoid type would show a better response to steroid therapy, either local or systemic, than the purely degenerative lesion of osteo-arthritis. The difference between our experience and that of others in the local treatment of osteo-arthritis may reflect only the failure of other authors to conduct trials under controlled conditions. Miller, White, and Norton (1958), in a careful study of 181 patients with osteo-arthritis of the knees, were unable to detect any difference in response to the injection of lactic acid, novocaine, hydrocortisone, and saline. However, the first assessment following treatment was made 6 weeks after the course of injections, so that a less prolonged effect could not be measured.

Effect of Order of Injection.—Fearnley and others (1956), in a pilot study of intra-articular procaine and hydrocortisone acetate in rheumatoid arthritis, found that the first course of treatment conferred more benefit than the second, regardless of which drug was used. In this study of patients with osteo-arthritis this was evident in the effect on walking time. The percentage improvement in walking time after the first course was nine times greater than that after subsequent courses. Claims for improvement from single courses of treatment must therefore be evaluated cautiously in the light of this observation.

Placebo Response.—It was of interest that, although more patients experienced relief of pain after injection of the active compounds than after that of the placebo, in 36 per cent. of knees there was improvement from the inert material. If one-third improves with inactive material, great care must obviously be exercised in interpreting the results of uncontrolled studies of intra-articular therapy. The interesting problem of the placebo reactor has formed the basis of a further study of these patients by Morison, Woodmansey, and Young (1960). After preliminary psychological assessment a course of placebo tablets was given, on which 26 per cent. of patients improved, and 38 per cent. developed side-effects. Those who consistently showed no response to placebo injections or tablets displayed no side-effects from the inert preparations. This work suggests that a substantial reduction in the number of patients likely to benefit from inert preparations could be obtained by a preliminary study using placebo tablets; only those patients showing no side-effects would then be included in the subsequent trial. The group studied would then, of course, be selected. Alternatively, all patients would take part in the trial, which would then include a group of predicted reactors.

Complications.—There were few complications after intra-articular injection. In two knees there

was increased pain and stiffness which lasted 3 days; this local exacerbation has been noted by other workers (Kendall, 1958). In a trial of similar design involving 24 patients with rheumatoid arthritis, three patients developed deep vein thrombosis in the injected leg (Chandler, Wright, and Hartfall, 1958). This complication was not observed in any patient with osteo-arthritis; our experience is that deep vein thrombosis is a complication of rheumatoid disease, and it may be that its development in the injected leg was precipitated by intra-articular injection.

It was noted that, after prolonged intra-articular administration of hydrocortisone in rheumatoid arthritis, radiological deterioration, sometimes considerable, occurred in over half the knees so treated (Chandler and Wright, 1958). The development of relatively painless destruction of the hip joint in four patients treated with corticosteroids has since been described (Sweetnam, Mason, and Murray, 1960). Three of these patients received steroids systemically and one by intra-articular injection. Such deterioration, resembling Charcot's arthropathy, may also occur in osteo-arthritis after multiple (18) injections of intra-articular hydrocortisone (Chandler, Jones, Wright, and Hartfall, 1959), but this has not been our experience in the present trial, in which fewer injections of active compound were used.

Summary

The effect of intra-articular injections of hydrocortisone acetate and hydrocortisone *tertiary*-butylacetate (TBA) has been studied in 25 patients with osteo-arthritis whose main incapacity arose from involvement of the knees.

Each patient was given three courses of injections (hydrocortisone, TBA, and placebo) in random order. Each course consisted of four injections at fortnightly intervals, with 8 weeks' rest between courses. Pain, tenderness, walking time, range of joint movement, and limitation of extension were assessed every 2 weeks.

A transient lessening of pain followed the courses of active compounds, but no other significant benefit was derived. There was no significant difference between the results of the two drugs. Significant improvement in walking time occurred after the first course of treatment irrespective of its nature. Three patients experienced minimal complications. No radiological deterioration was observed in the knees injected.

36 per cent. of the knees improved from the inert material.

In a subsequent assessment of the effect of placebo tablets on these patients, 26 per cent. improved and 38 per cent. developed side-effects. Those consistently showing no response to placebo therapy displayed no side-effects.

We are indebted to Messrs. Merck, Sharp, and Dohme for a generous supply of hydrocortisone TBA. We are grateful to Sister P. R. Benson and her nursing staff for their co-operation. Dr. G. Watkinson and Dr. J. G. Dare gave helpful statistical advice.

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Traitement intra-articulaire dans l'ostéo-arthrite.—Comparaison de l'acétate d'hydrocortisone et du butylacétate tertiaire d'hydrocortisone

RÉSUMÉ

On a procédé à une étude sur l'effet des injections intra-articulaires d'acétate d'hydrocortisone et de butylacétate d'hydrocortisone (TBA) chez 25 malades atteints d'ostéo-arthrite, dont l'incapacité principale siegeait aux genoux.

Chaque malade a reçu, dans un ordre fortuit, trois séries d'injections: hydrocortisone, TBA et une substance inerte. Chaque série consistait de quatre injections bimensuelles, avec huit semaines de repos entre les séries. Toutes les deux semaines on recherchait: douleur spontanée, douleur provoquée à la palpation, temps de marche, amplitude du mouvement articulaire et limites de l'extension.

Une diminution temporaire de la douleur a suivi chaque série d'injections des substances actives, mais on n'a noté aucun autre avantage appréciable. On n'a pas observé de différence appréciable entre les effets des deux composés d'hydrocortisone. Une amélioration appréciable du "temps de marche" s'est produit après la première série d'injections, indépendamment de la substance administrée. Trois malades ont ressenti des complications peu importantes. On n'a pas observé de détériorations radiologiques dans les genoux injectés.

Trente-six pour cent des genoux ont manifesté une amélioration après avoir reçu la substance inerte. Au cours d'une évaluation subséquente de l'effet des comprimés-témoins sur ces malades, on a trouvé que 26 pour cent d'entre eux ont manifesté une amélioration et 38

pour cent des effets secondaires. Les malades qui ne réagissaient jamais thérapeutiquement à ces comprimés de substance inerte, n'accusaient pas d'effets secondaires.

Terapéutica intra-articular de ósteo-artritis.— Comparación del acetato de hidrocortisona y del butilacetato terciario de hidrocortisona

SUMARIO

Se realizó un estudio sobre el efecto de las inyecciones intra-articulares de acetato de hidrocortisona y de butilacetato terciario de hidrocortisona (TBA) en 25 enfermos con ósteo-artritis, cuya principal incapacidad residía en la afectación de las rodillas.

Cada enfermo recibió, en un orden determinado al azar, tres series de inyecciones: hidrocortisona, TBA y una substancia inerte de control. Cada serie consistió en cuatro inyecciones quincenales, con ocho semanas de descanso entre las series. Cada quincena se investigó: dolor espontáneo, dolor provocado a la exploración, tiempo caminando, amplitud del movimiento articular y limitación de la extensión.

Una pasajera disminución del dolor siguió a cada serie de inyecciones de compuesto activo, pero no se apreció otro beneficio significativo. No se notó diferencia apreciable entre los efectos de los dos compuestos de hidrocortisona. Una apreciable mejoría del "tiempo caminando" apareció después de la primera serie de inyecciones, independientemente de la substancia administrada. Tres enfermos experimentaron complicaciones mínimas. No se observó agravación de los signos radiológicos en las rodillas inyectadas.

El 36 por ciento de los enfermos aseguraron haber experimentado mejoría con la inyección de substancia inerte. En una investigación posterior del efecto de comprimidos postizos en dichos enfermos, 26 por ciento de ellos manifestó una mejoría y el 38 por ciento efectos secundarios. Los enfermos que repetidamente no presentaron ninguna respuesta terapéutica a estos comprimidos de substancia inerte, tampoco presentaron efectos secundarios.

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RHEUMATIC FEVER IN THE YOUNG ADULT

BY

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The clinical manifestations and course of rheumatic fever have been studied mainly in children. Recently a number of studies of this disease in military personnel have been reported (Gray, 1949; Carmichael, 1956; Bates, 1958; Slater and Rosenbaum, 1959). In these series, patients with a past history of rheumatic fever were included, which may have modified both the clinical manifestations and subsequent progress. The present paper deals with the characteristic features of rheumatic fever occurring for the first time in young adults.

Material

A series of 27 patients diagnosed as having rheumatic fever on the criteria of Duckett Jones (1944) were amongst more than one hundred admissions for acute arthropathy to a Service Hospital between 1956 and 1959. 26 of the patients were male and one female. Their ages varied between 15 and 23, the majority being in their late 'teens. Care was taken that no patients were included in this series who had a past history of rheumatic fever, chorea, or arthropathy of unknown cause. Because of the difficulty in differentiating between rheumatic fever and other allergic arthropathies, patients who had had prophylactic inoculations or symptoms suggestive of dysentery in the 8 weeks before admission were also excluded from this series.

Clinical and Pathological Findings

The family history of five patients (20 per cent.) indicated that one or both parents had suffered from rheumatic fever. Inquiry was made not only from the patient at the time of admission, but also in subsequent follow-up questionnaires to the family doctor and patient.

Patients with rheumatic fever were admitted throughout the year, but the incidence was highest in winter and early spring, over two-thirds of the cases occurring between February and May.

Of the 27 patients in the present study, 22 gave a recent history of sore throats, with an equal incidence in each of the 4 weeks before rheumatic fever developed. Five of these patients had been treated for their sore throats with penicillin (1,000,000 Units daily for 7 to 10 days). Of the five patients who had not had sore throats, four had raised antistreptolysin titres (370, 440, 600, and 800 Todd units per ml. respectively), and a heavy growth of beta-haemolytic streptococci of Lancefield Group A was cultured from the pharynx of the other.

Clinical Features of the Acute Attack

Anorexia, malaise, or other constitutional symptoms of rheumatic fever were uncommon, most of the patients feeling well throughout their illness. During the initial stages of their illness all cases had a pyrexia, commonly in the region of 99-102° F. Fever higher than this warranted reconsideration of the diagnosis; in one patient pneumonia, and in another streptococcal septicaemia, had complicated rheumatic fever. In several other patients, not included in this series, the arthropathy and high fever were due to osteomyelitis.

All the patients presented as cases of arthropathy. The arthropathy was usually of gradual onset, the knees or ankles being affected first in all cases. These together with the hip joints were the most commonly involved. It was very unusual for other joints to be affected, and in only five cases (15 per cent.) were the upper limbs involved. A striking feature was the mildness with which the majority of joints were involved. The degree of involvement varied considerably. In 24 patients the arthropathy consisted only of stiffness, slight swelling, and tenderness, and several of them being able to walk on the

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affected limb without undue discomfort. In only three patients were the joints severely affected, making walking impossible and causing loss of sleep. In about a third of the cases, only two joints were affected, and the arthropathy was seldom of the migratory type involving several joints successively. In one patient the left knee only was involved, but the presence of carditis and an anti-streptolysin-O titre of 800 Todd units together with a rapid symptomatic improvement on salicylate therapy was felt to justify his inclusion in the present series.

No patients had erythema marginatum, erythema multiforme, or erythema nodosa. No patients developed purpuric lesions. Skin nodules were noted in the occipital region in two patients. Two patients had transient splenic enlargement.

Cardiovascular Manifestations of Rheumatic Fever

Great care was taken to elicit any evidence of carditis. Because of the difficulty and variability of auscultatory findings in patients with rheumatic fever, each patient was examined daily during the acute stages of the illness, using the routine examination suggested by Parkinson and Hartley (1946). The results of their pre-service medical examination were available for comparison with the findings of the present study. (No patient in the present series had been noted to have any cardiovascular abnormality at his pre-service medical examination.) All patients had postero-anterior and lateral chest *x* rays at the time of admission and when indicated these were repeated and radiological screening carried out. An electrocardiograph was obtained on admission and once a week during the acute stages of the illness.

Initially all the patients had a tachycardia of between 90 and 120 per minute. With rest in bed and treatment this rapidly settled. 1 to 3 weeks after admission a sinus brachycardia of below 55 per minute was noted in ten cases (36 per cent.), and in five of these the pulse rate remained below 40 per minute for up to 5 days.

During the acute stages of the illness the majority of the patients had an apical systolic murmur. In all but eight patients, this was a short mid-systolic aortic ejection murmur, conducted to the apex. In eight patients the apical systolic murmur was considered to be organic, as it was of a loud blowing character, was well conducted to the axilla, and was pan-systolic embracing both heart sounds. At the time of admission three patients had an aortic diastolic murmur and two further cases developed this sign during the acute stages of the illness. At the time of discharge five patients still had an apical pan-systolic murmur, two an aortic diastolic murmur, and one an apical pan-systolic murmur together with an aortic diastolic murmur. No patient had an apical diastolic murmur (Table I).

TABLE I

INCIDENCE OF ORGANIC HEART MURMURS IN 27 PATIENTS OF THE PRESENT SERIES

Murmur	On Admission*	During Illness	On Discharge
Organic Apical Systolic ..	8	8	6
Aortic Diastolic	3	5	2

* No evidence of murmurs at pre-service medical examination.

No patient developed heart failure or clinical or radiological evidence of cardiac enlargement. No patient developed bacterial endocarditis. Two patients developed pericarditis soon after admission with retrosternal discomfort and a transient pericardial friction rub; this pericarditis was clinically of the fibrinous type, and neither case developed cardiac tamponade or other evidence of a pericardial effusion.

Electrographic abnormalities were noted in six patients. In one patient with pericarditis there was generalized S-T elevation and flattening of the T-waves. In five patients there was prolongation of the P-R interval above 0·22 seconds, and in one of these a Wenkebach AV block developed and persisted for 4 days.

It was considered that sixteen out of the 27 patients (60 per cent.) had evidence of carditis during their attack of rheumatic fever. The evidence for carditis rested on the presence of an abnormal murmur in twelve patients, the presence of pericarditis in two, the presence of a P-R interval of 0·24 and 0·28 in two, and the presence of a Wenkebach conduction defect in one. Only seven patients (26 per cent.) had evidence of cardiac involvement at the time of their discharge.

Results of Pathological Investigations

The erythrocyte sedimentation rate was raised above 40 mm./hr in all cases on admission, the highest levels being found in the first week and varying between 44 and 120 mm./hr. Subsequently the E.S.R. tended to settle slowly, though one patient had a second sharp elevation associated with a recurrence of the sore throat.

A full blood count was carried out at the time of admission on all patients. Anaemia was unusual,

only nine cases having a haemoglobin of less than 80 per cent. A surprising feature was the absence of leucocytosis. One patient had a white cell count of 11,600/c.mm., but in all other cases the total white cell count was less than 10,000/c.mm. No abnormalities in the white cell differential count were found.

Difficulty was experienced in obtaining positive throat cultures, Group A beta-haemolytic streptococci only being obtained in eleven cases (40 per cent.). This difficulty was attributed to the fact that several patients had been treated with penicillin before admission to hospital. Thus five patients had been given a full course of penicillin for the initial sore throats, and a further six had been started on oral penicillin at the time of onset of the arthropathy.

In those patients in whom streptococci of Lancefield's Group A were not isolated, antistreptolysin-O titres were measured. All sixteen patients in whom this estimation was carried out showed elevations of more than 200 Todd units per ml. The antistreptolysin-O levels varied between 220 and 1,800 Todd units per ml., the mean value on admission being 600 Todd units.

Management of the Acute Attack

The patients were, as far as possible, nursed together in a ward reserved for cases of rheumatic fever. This reduced the incidence of extraneous upper respiratory infection and improved morale.

The majority of the patients did not feel particularly ill at the time of admission, nor did they suffer much discomfort from their affected joints. In all but two cases prompt relief of symptoms was obtained by rest in bed, moulded splints, and salicylates. Initially each patient was given 2 g. sodium salicylate 4-hrly; once a satisfactory clinical response had occurred, or earlier if side-effects of salicylate treatment such as tinnitus, deafness, or hyperpnoea necessitated it, the dosage was lowered to 1·5 g. sodium salicylate 6-hrly.

Only two patients did not respond to this regime. Estimation of their serum salicylate levels showed 35 and 40 mg./100 ml. and further increases in the salicylate dosage produced marked side-effects. In these two patients salicylates were stopped and prednisolone (30 mg. daily) produced rapid relief. Subsequently the prednisolone was gradually replaced by salicylates without a relapse.

All patients were given oral phenoxymethyl penicillin (120 mg. twice daily) during their stay in hospital. In those patients with a positive throat culture for Group A beta-haemolytic streptococci an initial 10-day course of intramuscular procaine penicillin (600,000 Units daily) was given, and further throat swabs were taken. In one patient it was necessary to perform a tonsillectomy to prevent successive relapse from chronic tonsillar sepsis.

The erythrocyte sedimentation rate was used as a guide to the patient's management. Patients were not allowed up until the erythrocyte sedimentation rate had remained below 10 mm./hr for 3 successive weeks. During mobilization, which was of 4 to 6 weeks' duration, each patient was repeatedly advised on the need for penicillin prophylaxis for at least 3 years. In those patients with valvular disease, the importance of penicillin coverage during such operations as dental extractions was stressed.

Results of Follow-Up

Since nearly all patients with rheumatic fever are invalided from the armed services, their follow-up consisted of questionnaires sent to them, together with, when necessary, letters to their doctors.

The 27 patients in the present study were followed up for from 8 to 40 months. Despite the repeated advice regarding the necessity to take continuous antibiotic prophylaxis, only nine patients had continued to take penicillin regularly. These patients had had no further sore throats or joint pains, and had lost no time from work. Of the remaining eighteen patients, five had taken penicillin only intermittently, and thirteen had taken none. Of these eighteen patients, thirteen had had further episodes of sore throats and mild joint pains, though none had been diagnosed as having a further attack of rheumatic fever.

Discussion

There is no specific laboratory test for rheumatic fever, and its diagnosis rests mainly on clinical findings. Table II (opposite) compares the manifestations of acute rheumatic fever found in the present study with those in the reports of Bland and Duckett Jones (1951) and Lieber and Holoubek (1956).

The results of the present study, in which patients with a past history of the disease are excluded, compare closely with other reports of rheumatic fever in the young adult, in which patients with a past history of rheumatic fever have been included (Bates, 1958; Slater and Rosenbaum, 1959).

The clinical manifestations of rheumatic fever in the young adult differ in several important respects from those in children. Arthritis, the

TABLE II

MANIFESTATIONS OF ACUTE RHEUMATIC FEVER: COMPARISON OF REPORTS

		Military Personnel		All Ages	Children
Authors		Malpas and Landon	Bates	Lieber and Holoubek	Bland and Duckett Jones
Date		(1960)	(1958)	(1956)	(1951)
No. of Cases Studied		27	132	162	1,000
Major Manifestations (per cent.)	Carditis	60	56	56	63
	Arthritis	100	100	63	41
	Chorea	0	0	9	51
	Subcutaneous nodules	8	1	3	9
	Erythema marginatum	0	9	0·6	7
Minor Manifestations (per cent.)	Pyrexia	100	57	88	—
	Prolonged PR Interval	15	52	18	—
	Leucocytosis	0	56	86	—
	Erythrocyte Sedimentation Rate	100	100	—	—
	Preceding Sore Throat	80	73	56·2	—
	Antistreptolysin-O Titre over 200 (where performed)	100	82	—	—
	Previous Rheumatic Fever	0	15·1	39·5	
Evidence of Permanent Cardiac Damage		25	28	—	66

outstanding manifestation in young adults, was found by Bland and Duckett Jones (1951) to occur in only 41 per cent. of a large series of children, and in 63 per cent. of a series of patients of all ages (Lieber and Holoubek, 1956). Conversely, these workers found that chorea, which is rare in young adults, occurred in 51 per cent. of children. Evidence of carditis during the acute stages of rheumatic fever occurs in about 60 per cent. of young adults and children (Bates, 1958; Slater and Rosenbaum, 1959; Bland and Duckett Jones, 1951). Congestive cardiac failure, however, which occurs in about 20 per cent. of children, is rare in adults, and Bland and Duckett Jones report evidence of permanent cardiac damage in 66 per cent. of children, compared with only 25 per cent. in the present report and 28 per cent. in the report of Bates (1958) concerning rheumatic fever in American military personnel.

Rheumatic fever is frequently difficult to diagnose in the young adult. The mildness of the symptoms in the majority of patients in the present study, together with persistent evidence of cardiac damage in a quarter, underline the sinister form that the disease may take in this age group.

As Table II shows, chorea, erythema marginatum, and the presence of subcutaneous nodules, three of the five major criteria on which rheumatic fever may be diagnosed (Duckett Jones, 1944), are uncommon in young adults. The diagnosis of rheumatic carditis may also be difficult in this age group. Congestive cardiac failure and progressive cardiac enlargement seldom occur (Friedberg, 1959), while cardiac murmurs are frequently difficult to interpret, and pericarditis may have other aetiologies.

All the patients presented as cases of arthropathy. This was usually not severe, and in several cases involved only two joints. The arthropathy was seldom of a migratory type flitting from joint to joint, and in no case were the small joints of the hands or feet involved. These characteristics differ from the usual description of rheumatic polyarthritis in the adult, which is frequently severe, typically flits from one large joint to another, and may involve the small joints of the hand (Wood, 1956; Stollerman, 1960).

The diagnosis of rheumatic fever in the present study was made on the findings of polyarthritis, associated in 60 per cent. with evidence of carditis, together with such minor manifestations as fever, an elevated erythrocyte sedimentation rate, electrocardiographic changes, and evidence of recent streptococcal infection. Using the modified criteria of Duckett Jones (1944), at least one major and two minor manifestations of rheumatic fever must be present before the diagnosis can be made. Because polyarthritis, together with fever and a raised erythrocyte sedimentation rate, may be found in many other conditions, evidence of a recent Group A beta-haemolytic streptococcal infection was looked for carefully, and was considered essential for the diagnosis. In the present series the majority of patients had had a recent sore throat, and in all either a positive throat culture or a raised antistreptolysin-O titre (above 200 Todd units per ml.) was found. It was considered wise to treat all the

patients as having rheumatic fever rather than post-streptococcal arthritis as suggested by Friedberg (1959).

The seasonal incidence of rheumatic fever in the present study (Figure) differed slightly from that usually encountered (Coburn, 1931). This may in part be accounted for by the population group studied, namely entries of recruits doing their initial training.

All had a normal white cell count on admission and the absence of a leucocytosis is difficult to explain. In some this could have been due to their having been given antibiotics for the initial sore throat or at the onset of the arthropathy. It is of interest that five patients developed rheumatic fever despite receiving penicillin (1,000,000 Units daily for 7 to 10 days) within 1 or 2 days of the start of the initial sore throat. This agrees with the findings of Rammelkamp, Denny, and Wannamaker (1952) that treatment of the acute sore throat is less effective in the prevention of rheumatic fever than continuous prophylactic therapy.

The rarity of an apical diastolic murmur in adults is commented on by Friedberg (1959), and no patient in the present series developed a murmur of this type.

The management of rheumatic fever in this age group presented the difficulty that many patients suffered little discomfort from the disease and were anxious to be allowed out of bed. The initial eradication of Group A beta-haemolytic streptococci from the throat by full doses of penicillin was considered important, as this may lower the incidence of permanent cardiac damage (Vaisman, Rakita, Mortimer, Gudsch, Schuster, Vignau, Roberts, Krause, and Rammelkamp, 1958). The dose of procaine penicillin used (600,000 Units daily for 10 days) was adequate for this aim (Denny, Wannamaker, Brink, Rammelkamp, and Custer, 1950).

The use of corticosteroids rather than salicylates was not considered justified by recent experience (United Kingdom and United States Joint Report, 1955; Bywaters, 1956; Fischel, Frank, and Ragan, 1952), especially in view of the possible side-effects of these drugs (Smith and Good, 1956).

Despite repeated advice on the importance of prolonged and continuous antibiotic prophylaxis to prevent recurrence, only nine patients (33 per cent.) continued to take oral penicillin regularly after discharge. Of the remainder, 70 per cent. have had recurrent sore throats and occasional joint pains. This raises the question of the advisability of using monthly injections of the slowly absorbed repository benzathine penicillin, especially as this is a more effective means of obtaining continuous prophylaxis (Wood, Stollerman, Feinstein, Hirschfeld, Rusoff, Taranta, Haas, and Epstein, 1957).

Slater and Rosenbaum (1959) quote an incidence of rheumatic fever of 1 in 1,663 young military personnel. They found a particularly high incidence during the initial training period, and in the present series also 90 per cent. of the patients came from recruit camps. Excellent prolonged prophylaxis against streptococcal infections without serious hypersensitivity reactions has been obtained in the U.S. armed services with benzathine penicillin

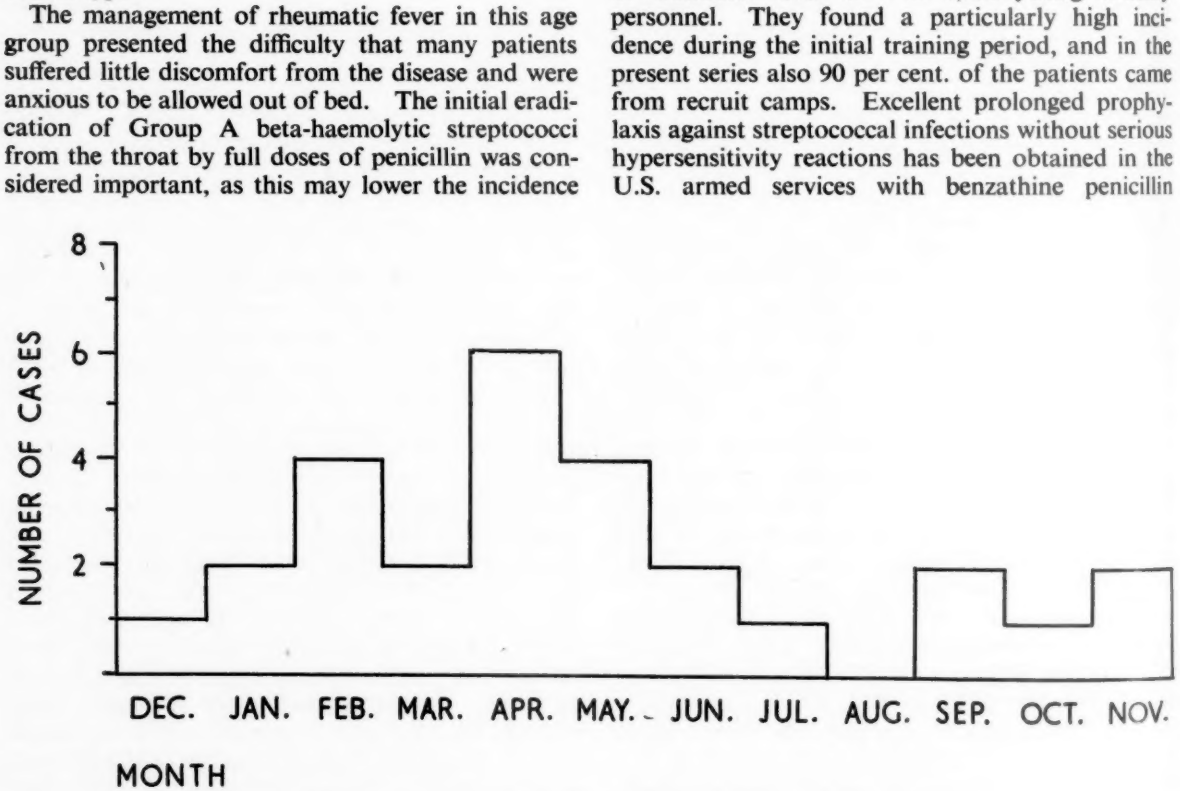

Figure.—Seasonal incidence of first attacks of rheumatic fever in 27 young adults.

(Sherwood, Gronbeck, and Denny, 1957). Such prophylaxis or short-term oral penicillin may well be indicated in Great Britain during recruit training.

Summary

The clinical manifestations of rheumatic fever occurring for the first time in 27 young adults are reported. The diagnostic difficulties are emphasized, as the occurrence of chorea, erythema marginatum, and subcutaneous nodules are uncommon, while the arthritis may be mild and is seldom migratory. The sinister form that rheumatic fever may take in patients of this age group is underlined by the fact that 60 per cent. had evidence of carditis during their illness, and 26 per cent. had significant cardiac murmurs on discharge. Those patients who took penicillin regularly in the 8 to 40 months of their follow-up had complete freedom from sore throats and joint pains.

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Rhumatisme articulaire aigu chez l'adulte jeune

RÉSUMÉ

On relate les manifestations cliniques du rhumatisme articulaire aigu apparaissant pour la première fois chez 27 jeunes adultes. On souligne les difficultés diagnostiques, car la chorée, l'érythème marginé et les nodules souscutanés sont peu communs, et l'arthrite peut être benigne et rarement migrante. La forme sinistre que le rhumatisme articulaire aigu peut revêtir chez des malades de cet âge se voit dans le fait que 60 our cent d'entre eux présentaient des signes de cardite pendant la maladie et que 26 pour cent manifestaient des souffles cardiaques organiques au moment de leur renvoi de l'hôpital. Les malades qui recevaient de la pénicilline régulièrement pendant les 8 à 40 mois d'observation étaient tout à fait libres d'angines et de douleurs articulaires.

Reumatismo poliarticular agudo en el adulto joven

SUMARIO

Se relatan las manifestaciones clínicas del reumatismo poliarticular agudo apareciendo por primera vez en 27 adultos jóvenes. Se resaltan las dificultades diagnósticas debidas al hecho de que la corea, el eritema marginado y los nódulos subcutáneos son de infrecuente aparición, a la vez que la artritis puede ser muy benigna y raramente migratoria. La gravedad que la fiebre reumática puede asumir en enfermos de esta edad es demonstrada por el hecho de que el 60 por ciento presentó signos de carditis durante la enfermedad y el 26 por ciento manifestó soplos cardiacos patológicos a ser dados de alta. Los enfermos que recibieron penicilina regularmente durante los 8 a 40 meses de observación estuvieron completamente libres de infecciones de la garganta y dolores articulares.

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SPIRO-ERGOMETRY IN PATIENTS SUFFERING FROM BECHTEREW'S DISEASE

BY

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Rogan, Needham, and McDonald (1955) performed lung-function tests on patients suffering from Bechterew's disease; their studies did not, however, include measurements during exercise.

Julian, Travis, and Bayles (1959) also performed lung-function tests at rest only, but they advocated investigations during strain. Renzetti, Nicholas, Dutton, and Jivoff (1960) mention the occurrence of hyperventilation of patients with Bechterew's disease during exercise, but they did not describe how the exercise was performed.

The functional condition of an organ or organic system is best evaluated when this organ or system is submitted to a certain degree of strain.

Spiro-ergometry has therefore been carried out in this clinic since 1954 in a group of patients suffering from Bechterew's disease, and the following questions were considered:

(*a*) To what extent do patients with Bechterew's disease differ from normal subjects?
(*b*) How should this difference be explained?
(*c*) What is the prognosis for the patients?

Material and Methods

The group consisted of 29 male patients with typical Bechterew's disease. They showed no evidence of pulmonary or cardiac disease, as judged from their history and normal routine physical examination. The average age at the time of onset of symptoms was 31 years, and the average duration of disease was 12½ years. The sacro-iliac joints showed ankylosis in seventeen, rosary formation in four, and sclerosis in seven. The Rose-Waaler sheep cell agglutination test was positive in two and negative in 26 cases, and was not done in one case.

Spiro-ergometry was carried out with the aid of a bicycle-ergometer, the patient being connected with a spirograph.*

The patient breathed room air during the experiment; the oxygen uptake was supplemented by means of a stabilizer. The patients were submitted to a strain of 90, 100, 120, 130, 140, and 150 Watt (1 Watt = 0·102 kg./sec.).

The oxygen uptake, respiratory frequency, tidal air (taken from the tracings on the spirograph), respiratory minute volume (frequency × tidal air), and respiratory equivalent (respiratory minute volume, in litres, required for 100 ml. oxygen uptake) were recorded. The results were then converted to correspond with a barometer pressure of 760 mm. Hg, at a dry temperature of 0° C., and were compared with those obtained in a similar manner from a control group of 23 volunteers, who were all normal males of the same age group as the patients with Bechterew's disease. The findings were statistically elaborated as described by Hill (1950).

Results (Table, opposite)

The oxygen uptake in patients with Bechterew's disease did not differ from that of normal subjects submitted to the same strain (Fig. 1, opposite). Nor did the two groups differ in respiratory minute volume (Fig. 2, opposite), or in the respiratory equivalent, which indicates the quantity of air (in litres) required for an oxygen uptake of 100 ml. (Fig. 3, opposite).

If the respiratory equivalent is a reliable index of the adequacy of the ventilation—as is sometimes incorrectly maintained—then these results would suggest that the adequacy of ventilation during strain was the same in the Bechterew patients as in the normal subjects.

As the Table shows, however, the respiratory frequency in Bechterew patients exceeded that in normal subjects (Fig. 4, overleaf), whereas the tidal air showed the reverse (Fig. 5, overleaf).

This indicates that respiration of Bechterew patients is rapid and shallow as compared with that of the controls.

* This was the valveless blower-spirograph of Lode, designed by Prof. M. N. J. Dirken, M.D.

TABLE

RESULTS OF SPIRO-ERGOMETRY IN 29 MALE PATIENTS WITH BECHTEREW'S DISEASE

Effort (Watt)	Frequency			Tidal Air (ml.)			Minute Volume (l.)			Oxygen Uptake (ml.)			Respiratory Equivalent		
	Normal	Bechterew	S.E.	Normal	Bechterew	S.E.	Normal	Bechterew	S.E.	Normal	Bechterew	S.E.	Normal	Bechterew	S.E.
90	19	22·3	1·3†	1432	1331	75	29·1	29·4	2·1	1270	1295	42	2·25	2·28	0·16
110	20·7	25·4	1·3‡	1673	1346	88†	34·5	34·0	2·5	1420	1420	45	2·38	2·42	0·30
120	20·3	26·5	1·4‡	1770	1447	84‡	36·9	37·3	2·6	1550	1530	68	2·44	2·43	0·15
130	22	27	1·6‡	1694	1455	115*	37·1	39·2	1·8	1590	1630	65	2·37	2·45	0·14
140	22·7	26·1	1·55*	1816	1543	104*	40·1	39·4	3·6	1740	1690	73	2·45	2·32	0·17
150	22·4	28	2·2*	1778	1632	119	39·4	44·5	3	1776	1730	49	2·20	2·50	0·13*

Significant:
* difference greater than twice standard error of difference.
† difference greater than 2½ times standard error of difference.
‡ difference greater than three times standard error of difference.

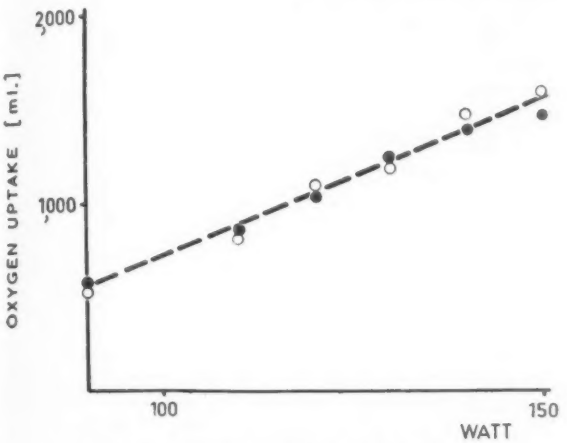

Fig. 1.—Oxygen uptake in relation to amount of work.
Open circles: Normal.
Closed circles: Bechterew.

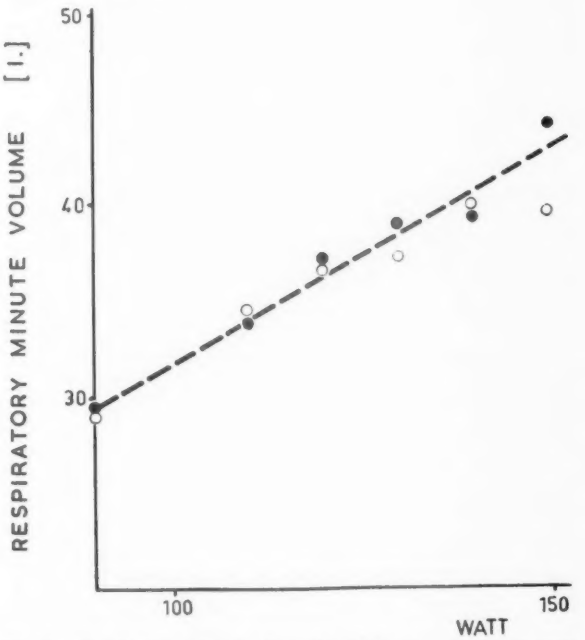

Fig. 2.—Respiratory minute volume in relation to amount of work.
Open circles: Normal.
Closed circles: Bechterew.

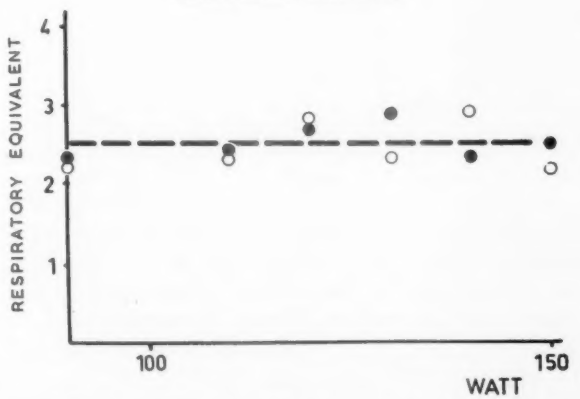

Fig. 3.—Respiratory equivalent in relation to amount of work.
Open circles: Normal.
Closed circles: Bechterew.

Discussion

The question arises why Bechterew patients adopt this respiratory pattern, which resembles that seen in cases of hyperventilation. Marshall, McIlroy, and Christie (1954) used the tidal air and the simultaneously determined pressure in the oesophagus to calculate the quantity of energy required for respiration under various conditions. Their findings show that respiration is always regulated by frequency and tidal air, and that the quantity of energy expended in this way is the smallest possible. The amount of energy used depends, among other things, on the tidal air. Since the lungs constitute an elastic system, a larger tidal air requires the overcoming of a larger elastic resistance. Increased rigidity of the lungs (through pulmonary congestion or fibrosis) causes a further increase in the elastic resistance which has to be overcome for the same amount of tidal air. To reduce this respiratory effort to a minimum, such patients prefer shallow breathing, which reduces the effort to overcome elasticity, and the required respiratory minute volume is obtained

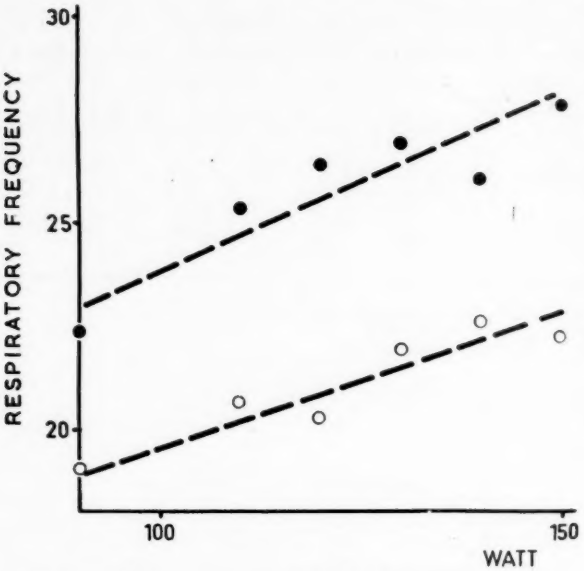

Fig. 4.—Respiratory frequency in relation to amount of work.
Open circles: Normal.
Closed circles: Bechterew.

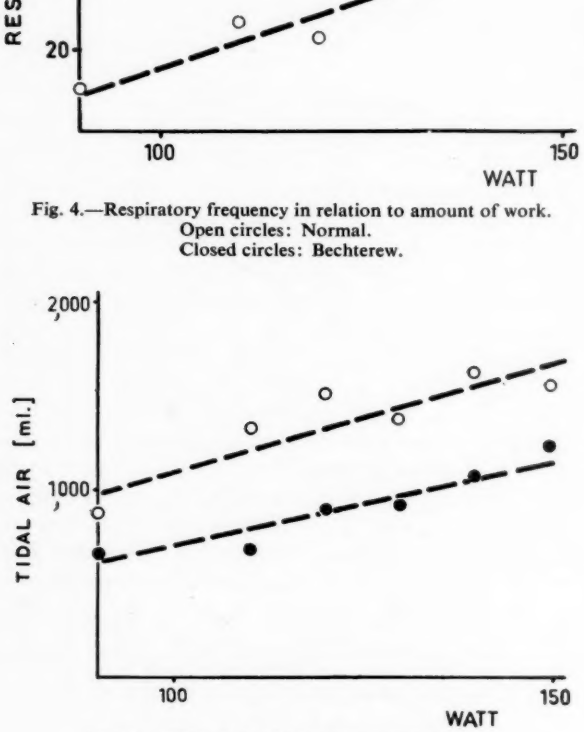

Fig. 5.—Tidal air in relation to amount of work.
Open circles: Normal.
Closed circles: Bechterew.

by increasing the frequency. As a result, the dead space is more frequently added to the alveolar ventilation, and the total respiratory minute volume increases; this in its turn causes an increase in the friction resistance of the air in the air passages, and, therefore, in the viscous component of the effort. Every patient adjusts his respiration so as to ensure that the sum of elastic effort and viscous effort is the smallest possible.

Julian, Travis, and Bayles (1959) found no increased rigidity of the lungs in four patients with Bechterew's disease.

Apart from these intrathoracic factors, there are probably a number of extrathoracic factors, which help to determine the type of respiration adopted to keep the ultimate respiratory effort as small as possible. One of these factors is the force required to move the ribs in the *costovertebral* joints, though this has not yet been proved.

These considerations may explain why Bechterew patients tend to breathe less deeply but rather with a slightly higher frequency. The mechanism by which respiration is adjusted so as to require the least possible effort is not known with certainty. It is possible that it involves reflexes originating from lungs, and perhaps from the muscles and ligaments. The investigations of Mead (1959) suggest that it is the mean force to be exerted by the respiratory muscles which determines the optimum rate of breathing.

In assessing the effects of this type of respiration on the patient, it must be borne in mind that the total respiratory minute volume consists of an effective respiratory minute volume, which forms the alveolar ventilation, and a component referred to as "dead space ventilation". The extent of the latter is dependent on:

(*a*) The size of the dead space. As the lung volumes in patients with Bechterew's disease are usually diminished, there are no reasons to suspect that the anatomic dead space in these cases is greater than normal. Renzetti, Nicholas, Dutton, and Jivoff (1960) found that the physiological dead space was greater than normal, because of an unequal ventilation-bloodflow ratio (Comroe, Forster, Dubois, Briscoe, and Carlsen, 1955). An unequal ventilation-bloodflow ratio was seen in only one of our fourteen patients, and this was thought to be due to the presence of Bechterew's disease. We agree with Renzetti and others (1960) that an increased physiological dead space may sometimes exist, but it seems to us that this is the exception rather than a rule.

(*b*) The frequency of respiration.

If the *total respiratory minute volume* in Bechterew patients equals that in normal subjects and their *respiratory frequency* is higher, then the dead space ventilation in these patients must be larger, and the alveolar ventilation consequently smaller, which means that they are in a state of hypoventilation.

Thus, the apparent tendency to hyperventilation in Bechterew patients proves to be in fact a tendency to hypoventilation, as suggested by Julian, Travis, and Bayles (1959). This seems to be confirmed by the fact that the carbon dioxide concentration of the alveolar air of eight patients suffering from Bechterew's disease (as measured by means of an infra-

red CO_2-analyser: Capnograph Godart-Mijnhardt) was 0·5-1·5 per cent. higher than in normal test subjects during exercise.

Summary

Spiro-ergometric examination during an effort of 90-150 Watt revealed that the oxygen uptake, respiratory minute-volume, and respiratory equivalent in 29 patients with Bechterew's disease did not differ significantly from the values obtained under identical conditions in 23 control subjects.

The patients' respiration, however, proved to be significantly shallower and more rapid. The dead space ventilation (frequency × dead space) was consequently larger than normal, while the alveolar ventilation was smaller than normal. Consequently there was a tendency to hypoventilation. The cause of the anomalous respiratory pattern is probably due to the instinctive attempt to reduce the respiratory effort to the minimum possible; the impaired movement of the ribs in the costo-vertebral joints is possibly of importance in this respect.

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Spiro-ergométrie chez des malades atteints de maladie de Bechterew

RÉSUMÉ

Des examens spiro-ergométriques pendant un effort de 90-150 watts révélèrent que l'absorption d'oxygène, le volume/minute respiratoire et l'équivalent respiratoire dans 29 cas de maladie de Bechterew ne se distinguaient pas d'une manière significative des chiffres obtenus chez 23 témoins en des conditions identiques.

La respiration de ces malades, cependant, fut appréciablement plus superficielle et plus rapide. La ventilation de l'espace résiduel (fréquence × espace résiduel) fut, par cóséquent, supérieure à la normale, tandis que la ventilation alvéolaire fut inférieure à la normale. Il y eut donc une tendance à l'hyperventilation. Ce type de respiration anormale est dû probablement à une tentative de réduire instinctivement l'effort respiratoire au minimum possible; la mobilité réduite des côtes au niveau des articulations costo-vertébrales y joue probablement un rôle important.

Espiro-ergometria en pacientes con enfermedad de Bechterew

SUMARIO

Exámenes espiro-ergométricos durante un esfuerzo de 90-150 vatios demostraron que la absorción de oxígeno, el volumen/minuto respiratorio y el equivalente respiratorio en 29 casos con enfermedad de Bechterew no presentan ninguna diferencia significativa con los valores obtenidos en 23 sujetos testigos en idénticas condiciones.

Sin embargo, la respiración de los pacientes se reveló significativamente menos profunda y más rápida. La ventilación del espacio residual (frecuencia × espacio residual) fué consecutivamente mayor que la normal, mientras que la ventilación alveolar fué inferior a la normal, hubo por tanto cierta tendencia a la hipoventilación. Este tipo anómalo de respiración es probablemente debido a una instintiva tendencia a reducir al mínimo posible el esfuerzo respiratorio; es posiblemente importante a este respecto la movilidad reducida de las costillas a nivel dela articulaciones costo-vertebrales.

Ann. rheum. Dis. (1960), **19**, 272.

INACTIVATION TEST OF THE LUPUS ERYTHEMATOSUS (L.E.) PLASMA FACTOR

BY

GEORGE BENCZE

From the First Department of Medicine, University Medical School, Szeged, Hungary
(Director: Prof. M. Julesz)

The existence of two types of lupus erythematosus (L.E.) plasma factor—transferable and non-transferable—has been suggested by our experiments with lupus erythematosus plasma transfer *in vivo* (Bencze, Kovács, and Cserháti, 1959; Bencze, Lakatos, and Ludányi, 1960).

Our further experiments *in vitro* showed differences between the two types of lupus erythematosus factor. These investigations, performed simultaneously with leucocytes from the subject and from other persons have shown that the L.E. factor of the non-transferable type does not produce the L.E. phenomenon, unless the subject's own leucocytes are used; this phenomenon could not be observed at all, or occurred to a much less extent, with leucocytes from other subjects (Bencze and Lakatos, 1960).

The present paper reports a further series of experiments *in vitro*, having in view the inactivation of the L.E. plasma factor. Earlier observations have shown that the inactivation of the L.E. plasma factor occurs at 59 and 65° C. respectively (Hargraves, 1949; Haserick, 1950).

Methods

(1) Plasma obtained from ten patients with L.E.-positive systemic lupus erythematosus (S.L.E.) was heated for 30, 60, 120, and 240 min. at + 56° C. 2 ml. of each batch of this plasma was added to the subjects' own leucocytes (washed six times in 240-ml. physiological saline) and to leucocytes obtained from normal persons. Subsequently the L.E.-cell test was performed by the rotatory method of Zinkham and Conley (1956).

(2) The usual L.E.-cell examination was done simultaneously in every case as a control test by Zinkham and Conley's rotatory method. Additional L.E.-cell tests were made with the patient's own washed leucocytes not supplemented with plasma, by Zinkham and Conley's rotatory method, to check the proper washing of the leucocytes.

(3) 2 ml. transferable plasma collected from each of three S.L.E. patients was kept for 30 and 60 min. respectively at +65° C.; they all coagulated within 30 min. The coagulated plasma was broken up with a glass stick and added to normal leucocytes. Subsequently the L.E.-cell test was done by Zinkham and Conley's rotatory method.

(4) Plasma obtained under sterile conditions from three S.L.E. patients was heated at +56° C. for one hour and transfused to dogs in doses of 1 and 2 ml./kg. body weight respectively, as described in our earlier report (Bencze and Ludányi, 1960).

Results

Several inactivation tests were performed with plasma obtained from ten different S.L.E. patients, and with the pleural effusion of one such subject. The tests were repeated at least six times with plasma from each patient. The L.E.-cell phenomenon was seen when three batches of L.E. plasma factor of transferable type were used, both with the subject's own leucocytes and leucocytes from other persons, even with plasma kept at 56° C. for 4 hours. In all cases identical amounts of L.E. cells were present, as with plasma not exposed to heat. These three batches of S.L.E. plasma produced the L.E.-cell phenomenon, even when heated at +65° C. for 30 and 60 min. respectively, when the plasma also coagulated with leucocytes from other persons. One of these patients developed polyserositis. The L.E.-cell phenomenon was also seen when the pleural effusion was added to leucocytes from other persons. This pleural effusion was not inactivated when heated at 56° C. for 2 hours; the L.E. cells were seen in unchanged amounts when it was added to leucocytes from other persons.

Plasma from the other seven S.L.E. patients was inactivated, however, in 30 min. at 56° C.; no L.E. cells were seen even when it was added to the subject's own washed leucocytes (Table, opposite, Cases 4 to 10).

Plasma transfer experiments were carried out on dogs with plasma from five of the seven S.L.E. patients; all proved to be non-transferable (Table, Cases 4 to 8). *In vitro* L.E.-cell investigations, however, showed the presence of the L.E.-cell phenomenon in two patients only with their own leucocyctes (Table, Cases 9 and 10). Using other leucocytes, no L.E. cells, or hardly any, were pro-

TABLE

TRANSFER OF L.E. CELLS AFTER EXPERIMENTAL INACTIVATION BY HEATING

Experiments		*In vitro*												*In vivo* Transfer to Dogs	
Source of Leucocytes		Plasma							Pleural Effusion	Plasma		Fresh Plasma		Heated Plasma	Fresh Plasma
		Subject's Own				Others			Others	Others		Own	Others		
Temperature (°C.)		56				56			56	65		Nil		56	Nil
Heating Time (min.)		30	60	120	240	30	120	240	120	30	60	Nil		60	Nil
Case No.	1	+	+	+	+	+	+	+	—	+	+	+	+	T	T
	2	+	+	+	+	+	+	+	—	+	+	+	+	T	T
	3	+	+	+	+	+	+	+	+	+	+	+	+	T	T
	4	0	0	0	—	0	—	—	—	—	—	+	±	—	NT
	5	0	0	0	—	0	—	—	—	—	—	±	±	—	NT
	6	0	0	0	—	0	—	—	—	—	—	+	±	—	NT
	7	0	0	0	—	0	—	—	—	—	—	±	±	—	NT
	8	0	0	0	—	0	—	—	—	—	—	±	±	—	NT
	9	0	0	0	—	0	—	—	—	—	—	±	0	—	—
	10	0	0	0	—	0	—	—	—	—	—	+	0	—	—

— = No experiment.
\+ = L.E. cells seen.
0 = L.E. cells not seen.
T = Transferable.
NT = Non-transferable.
± = L.E. cells sometimes seen, sometimes not seen.

duced in the other five patients, even when a large amount of plasma was added.

When we transfused three batches of S.L.E. plasma of the transferable type kept at 56° C. for 60 min. into dogs, we succeeded in producing L.E. cells in the same way as with plasma not exposed to heat (Table, Cases 1 to 3).

Discussion

Additional differences between the two types of L.E. plasma factor were demonstrated by L.E. plasma factor inactivation tests. We failed to confirm findings reported in the literature concerning the inactivation of the L.E. plasma factor. Our investigations showed that the transferable type of L.E. plasma factor was not inactivated even when heated at 65° C., whereas the L.E. plasma factor of the non-transferable type was destroyed when heated at 56° C. for 30 min.

Summary

In vitro inactivation experiments were carried out with plasma from ten different patients with systemic lupus erythematosus. Three batches of L.E. plasma factor of the transferable type failed to become inactivated, even when heated at 65° C. for 30 min. Seven batches of L.E. plasma factor of the non-transferable type became inactivated, however, when heated at 56° C. for 30 min.

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Réaction d'inactivation du facteur L.E. du plasma

RÉSUMÉ

On effectua des expériences d'inactivation *in vitro* avec du plasma provenant de dix malades atteints de lupus érythémateux généralisé. Trois lots du facteur plasmatique L.E. du type transferable n'ont pas pu être inactivés, même à une température de 65° C. pendant 60 minutes. On est arrivé, cependant, à inactiver sept lots du facteur plasmatique L.E. du type non-transferable en les soumettant à une température de 56° C. pendant 30 minutes.

Reacción de inactivación del factor L.E. del plasma

SUMARIO

Se llevaron a cabo experimentos de inactivación *in vitro* con plasma procedente de diez enfermos con lupus eritematoso generalizado. Tres muestras del factor L.E. del plasma del tipo transferible no llegaron a inactivarse, aun siendo sometidas a una temperatura de 65° C. durante 60 minutos. Siete muestras del factor L.E. del plasma del tipo no transferible resultaron inactivadas sin embargo, cuando se sometieron a una temperatura de 56° C. durante 30 minutos.

Ann. rheum. Dis. (1960), **19**, 274.

BOOK REVIEWS

Rheumatic Fever. Epidemiology and Prevention. Edited by R. Cruickshank and A. A. Glynn. 1959. Pp. 193. Blackwell Scientific Publications, Oxford. (25*s.*)

This book consists of the papers given at a Symposium on the Epidemiology and Prevention of Rheumatic Fever, held at the International Children's Centre in Paris in 1956.

Shortly after the French report had gone to press, the editor, Dr. R. Gautier, died suddenly, so that the editing of the English edition was undertaken by Prof. Cruickshank and Dr. Glynn. This is divided into four main sections: the biology of group A haemolytic streptococci, the epidemiology of infection with group A haemolytic streptococci, the epidemiology of rheumatic fever, and the prevention of rheumatic fever. Each section contains contributions by workers in that field, together with discussions. As must be expected in a Symposium of this nature, the length and quality of the papers varies, but the general standard is high.

In the first part of the biology of group A haemolytic infection, as well as a general review of the subject, there is useful information on methods. The epidemiology of streptococcal infection in various countries is well documented. In the section on epidemiology of rheumatic fever there is a comprehensive review of the evidence for the relationship of group A streptococci infection to this disease by Dr. M. McCarty of New York, and other factors, such as host immunological reactivity, environment, heredity, etc., are well discussed. In the section on prevention of rheumatic fever, Dr. M. Finland of Boston gives a valuable review of the problems raised by chemotherapy. He stresses that there has been no significant increase in the degree of resistance in any of the beta haemolytic or viridans streptococci, and that penicillin and sulphonamides would appear to be the most suitable antibiotics for therapy, and although, as yet, the role of the long-acting sulphonamides has not been worked out, these may be very useful. This paper is followed by authoritative reports and discussion on prophylaxis. The problem of the first attack and its prevention is also considered and while the value of treating overt streptococci infection is well recognized, more research is required in this field.

As the reports in this book on the various aspects of rheumatic fever come from most European countries and the United States of America, it gives a good review of the present knowledge of the haemolytic streptococci and its relationship to rheumatic fever, as well as indicating methods of prevention. B. M. ANSELL.

Lehrbuch der Rheumatologie. By H. Tichy, K. Seidel, and G. Heidelmann. 1959. Pp. 447, 136 figs. V. E. B. Verlag, Berlin. (*D.M.* 32.70.)

This textbook comes from the Eastern zone of divided Germany (Dresden, Leipzig, and Meiningen). Its comprehensive nature may be gauged from the inclusion of separate chapters on physiotherapy, rehabilitation, statistics, surgery, etc. The authors have avoided grinding any particular medical axe of their own, have set out all points of view fairly, and have given the reader ample information to make up his own mind. As is inevitable in such a procedure, the close text and wealth of detail tend to make the reader's attention wander. A little judicious pruning and re-arrangement of text would soon remedy matters; for example, several pages of prescriptions in common use could safely be left out; while references at the end of each chapter may have some advantage they cause reduplication and lead to inevitable increase in bulk.

Although there are more references to Soviet literature than is customary in Western textbooks, it is only fair to add that the bibliography is truly international and more than adequate. But can one write behind the "iron curtain" without a small political shadow darkening the pages? A valiant attempt in this direction has undoubtedly been made here, but was it not Lloyd George who once said of a political opponent—"he has sat on the fence for so long that the iron has entered his soul"? In this case it is probably not bitterness but some other motive which has led to the omission of every watering place in France, Britain, and Italy from the list of the "most important spas". Such an oversight would be strange in this book with its wealth of detail, but has been counterbalanced by leaving out the Russian spas, about which so little is known (assuming that they exist).

A good deal of attention is devoted to indexing, with separate acknowledgment to authors of monographs and textbooks, and to journals specializing in the rheumatic diseases; there is an index of authors and subject matter. In spite of minor lacunae the volume is a tribute to the industry and scholarship of its authors and to the indisputable fact that medicine knows no frontiers.

DAVID PREISKEL.

Ann. rheum. Dis. (1960), **19**, 275.

AUSTRALIAN RHEUMATISM ASSOCIATION

The third annual general meeting was held in Melbourne in October, 1959, when the following officers were elected for the year 1960:

President:	Dr. George McEwen
Senior Vice-President:	Dr. A. T. Pearson
Vice-President:	Dr. Brian Haynes
Hon. Secretary:	Dr. Ray Robinson
Hon. Treasurer:	Dr. Roderick Strang

There are now seventy members, including all the doctors who are members of the arthritis clinics of the general hospitals of Australia, and the association meets once a year in one of the capital cities. The 1960 meeting will be held in Canberra. There are three regional groups which meet three or four times a year: New South Wales (including members from Queensland), Victoria (including members from South Australia and Tasmania), and Western Australia. The second issue of the *N.S.W. Group Report* (vol. 1, December, 1959) contains several of the papers given at the annual meeting in 1959.

The Parr Rheumatic Prize (50 guineas), awarded triennially for the best work published in Australia during the preceding three years, will be judged at the end of 1960.

SOCIEDAD MEXICANA DE REUMATOLOGIA

Officers, 1960

President: Dr. Alfonso Chavez S.
Secretary: Dr. Aurelio Gutierrez Moyano
Treasurer: Dr. Manuel Boelsterly

Committee Members:
Dr. J. Perez Mata (*Tampico, Tams.*)
Dr. H. Rodriguez (*Guadalajara, Jal.*)

ROYAL COLLEGE OF PHYSICIANS OF LONDON

COMMITTEE ON CHRONIC RHEUMATIC DISEASES

The President of the Royal College of Physicians has appointed a Committee to consider the needs of rheumatology in relation to the National Health Service, in particular as regards the provision of additional treatment and training facilities. The members are as follows:

Sir Robert Platt, Bt., M.D., LL.D., P.R.C.P.
William Sydney Charles Copeman, O.B.E., M.D., M.R.C.S., F.R.C.P. (*Chairman*).
Ernest Thomas Conybeare, O.B.E., M.D., M.R.C.S., F.R.C.P.
George Durant Kersley, T.D., M.D., M.R.C.S., F.R.C.P. (*Hon. Secretary*).
Francis Dudley Hart, M.D., F.R.C.P.
Eric George Lapthorne Bywaters, M.R.C.S., F.R.C.P.
Jonas Henrik Kellgren, F.R.C.S., F.R.C.P.
Frank Sebastian Cooksey, O.B.E., M.D., F.R.C.P.
Oswald Arthur Savage, O.B.E., M.R.C.S. F.R.C.P.
William Derrick Coltart, F.R.C.S.

Ann. rheum. Dis. (1960), **19**, 276.

ABSTRACTS

This section of the ANNALS *is published in collaboration with the two abstracting Journals,* ABSTRACTS OF WORLD MEDICINE, *and* OPHTHALMIC LITERATURE, *published by the British Medical Association.*

The abstracts selected for this Journal are divided into the following sections: Acute Rheumatism; Chronic Articular Rheumatism (Rheumatoid Arthritis, Osteo-Arthritis, Spondylitis, Miscellaneous); Disk Syndrome; Gout; Pararheumatic (Collagen) Diseases; Non-Articular Rheumatism; General Pathology; ACTH, Cortisone, and other Steroids; Other General Subjects. At the end of each section is a list of titles of articles noted but not abstracted. Not all sections may be represented in any one issue.

The section "ACTH, Cortisone, and other Steroids" includes abstracts and titles of articles dealing with research into the scope and modus operandi *of steroid therapy.*

Acute Rheumatism

Pathogenic Staphylococci in a School Population treated with Antibiotics for the Prophylaxis of Rheumatic Fever. (Les staphylocoques pathogènes dans une collectivité d'écoliers, traités aux antibiotiques, en vue de la prophylaxie de la maladie rhumatismale.) BALDOVIN-AGAPI, C., BADENSKI, A., MIHALCO, F., IONESCO, M., CHIRESCO, M., and BORȘAL, L. (1959). *Arch. roum. Path. exp. Microbiol.*, **18**, 435. 2 figs, 12 refs.

During an epidemic of streptococcal tonsillitis the adolescent pupils of a large school in Bucharest were treated either with penicillin or with sulphathiazole for one month, largely for the prevention of rheumatic fever. Over half the pupils were resident. Throat and nasal swabs were taken before, during, and after treatment. Pathogenic staphylococci, which were further identified by lysotyping, were found in approximately one-fifth of the pupils at all stages, being rather more common in resident (22 per cent.) than in non-resident pupils (15 per cent.). Nasal carriers were three times commoner than throat carriers.

Chemotherapy led to a progressive increase in the proportion of resistant staphylococci from 6 to 40 per cent. with penicillin, and from 18 to 87 per cent. with sulphathiazole. After the end of the period of treatment, 34 per cent. of the carriers of mostly resistant staphylococci got rid of these organisms by their own defences. Phagetyping showed most of the staphylococci belonged to Group 1, Type 80. The proportion of these increased with time and they were most frequently associated with a prolonged carrier state, but gave rise to no important clinical manifestations. *John Lorber.*

Toxigenicity of Group-A Streptococci isolated from Patients with Rheumatic Fever. (Toxigenicidad de los estreptococos grupo A aislados de enfermos con fiebre reumatica.) ORTIZ MASLLORÉNS, F., and ALÉS REINLEIN, J. M. (1959). *Rev. clin. esp.*, **75**, 153. 3 figs, 18 refs.

At the Institute for Clinical and Medical Research, Madrid, streptolysin-O, streptokinase, and proteinase production was quantitatively assayed in haemolytic streptococci of Group A isolated from 25 patients with rheumatic fever, ten patients with acute streptococcal infection without symptoms or signs of rheumatic fever, and 25 normal subjects and patients who were streptococcal carriers. The amounts of these substances produced showed similar variations in all three groups. Thus no evidence was obtained relating the clinical manifestations of rheumatic fever to the toxigenicity of the Group-A streptococci present. *M. Lubran.*

ABO Blood Groups and Secretor Character in Rheumatic Carditis. CLARKE, C. A., MCCONNELL, R. B., and SHEPPARD, P. M. (1960). *Brit. med. J.*, **1**, 21. 7 refs.

A significant reduction in the incidence of blood Group O and a non-significant increase in the proportion of non-secretors of ABH was found in 263 patients with rheumatic carditis from the Liverpool area as compared with 16,057 controls. In a similar (unpublished) investigation at the Canadian Red Cross Memorial Hospital, Taplow, Glynn found a significant excess of non-secretors and a non-significant deficiency of Group O among 609 patients with rheumatic carditis as compared with 15,046 controls. On combining the results from the two series a significant increase in the incidence of the disease was found both in those who were non-secretors and in those who were not of Group O. The levels of significance, however, were not sufficient to allow this association to be regarded as certain and further data, especially of controls, are needed. If the reactions of haemolytic streptococci are materially affected by the secretor status of the host differences in virulence or growth rate may be shown *in vitro* depending on the amount of water-soluble blood-group substances present in the culture media. Work on these lines is proceeding. It is suggested that investigations of the ABO blood groups and secretor character in series of patients with uncomplicated streptococcal throat infections and acute nephritis might be of interest. *G. W. Csonka.*

Observations on Rheumatic Fever in the Adult. (Consideraciones acerca de la enfermedad reumatica en el adulto.) LOSADA L, M., GOIĆ G, A., MAI F, E., GONZALEZ W, H., and D'ACUÑA V, G. (1960). *Rev. méd. Chile*, **88**, 28. 8 refs.

Contribution to the Epidemiology, Clinical Aspects, and Prophylaxis of Rheumatic Fever in Childhood. (Beiträge zur Epidemiologie, Klinik, und Prophylaxe des rheumatischen Fiebers im Kindesalter.) LORENZ, E., and WENDLER, H. (1960). *Münch. med. Wschr.*, **102**, 1049. 3 figs, 48 refs.

Frequency and Parallelism of Changes in the Clinical and Laboratory Findings in a Group of 500 Rheumatic Children with and without Cardiopathy. (Sulla frequenza e sul parallelismo delle alterazioni cliniche e di laboratorio in un gruppo di 500 bambini reumatici con e senza cardiopatia.) BUCCIANTI, E., GRANATA, G., and MASSARI, F. (1960). *Osped. maggiore*, **48**, 3. 6 figs, 46 refs.

Bone Marrow in Rheumatic Fever in Children. (Szpik kostny w chorobie reumatycznej u dzieci.) WILKOSZEWSKI, E., DYSZY-LAUBE, B., and FILIPOWICZ, A. (1960). *Pediat. pol.*, **35**, No. 1, p. 1. 3 figs, 9 refs.

Capillary Permeability in Acute Rheumatism. (Die Kapillarpermeabilität bei akutem Rheumatismus.) CIHULA, J., and POLAK, J. (1960). *Z. ges. inn. Med.*, **15**, 396. 17 refs.

Treatment of Rheumatic Fever with Steroids. (Die Therapie des rheumatischen Fiebers mit Steroiden.) PALITZSCH, D. (1960). *Med. Mschr.*, **14**, 170. 5 figs, 26 refs.

Behaviour of C-Reactive Protein in Rheumatic Fever. (Studio sul comportamento della proteina C reattiva nella malattia reumatica.) BERARDI, G., and CAGINI, P. (1959). *Aggiorn. pediat.*, **10**, 787. 30 refs.

Significance of "Acute Phase Reactions" performed on the Same Sample of Blood in Infantile Rheumatic Fever. KOLTAY, M., and ÉBREY, B. P. (1960). *Ann. paediat. (Basel)*, **194**, 295. 7 figs, 22 refs.

Antistreptolysin-O Titre in Sydenham's Chorea. (L'Antistreptolysine O dans la chorée de Sydenham.) IONASESCO, V., and IONASESCO, G. (1960). *Presse méd.*, **68**, 958. 2 figs, 11 refs.

Antistreptolysin-O Titre in Rheumatic Fever. (Il titolo antistreptolisinico nell'infezione reumatica.) DI BELLA, M., and PUGLISI, G. (1959). *Aggiorn. pediat.*, **10**, 675. 6 figs, 87 refs.

Rheumatic Heart Disease without Previous Polyarthritis and the Incidence of Recurrence. (Cardiopatie reumatiche senza precedenti poliartritici e incidenza delle recidive.) ACAMPORA, E., and DEL GUERCIO, E. (1960). *Riv. med.*, **74**, 492. 15 refs.

Rheumatism and Coronary Insufficiency. (Gościec a niewydolność wieńcowa.) CZARNIECKI, W., and DORYWALSKI, T. (1960). *Pol. Arch. Med. wewnet*, **30**, 167. 2 figs, 56 refs.

Q-T Interval in Rheumatic Fever. (Délka úseku Q-T u revmatické horečky.) DUFEK, V., HÁŠA, J., and FUNK, Z. (1960). *Čas. Lék. čes.*, **99**, 644. 21 refs.

Chronic Articular Rheumatism (Rheumatoid Arthritis)

Antirheumatic Action of Chlorpromazine and Its Use when Discontinuing Cortisone Treatment in Rheumatoid Arthritis. GALLI, T., and CAVIGLIA, E. (1959). *Arch. interamer. Rheum.*, **2**, 461. 9 figs, bibliography.

The anti-rheumatic activity of chlorpromazine was studied at the Rheumatological Centre of the University of Genoa. In patients with rheumatoid arthritis or acute rheumatism receiving the drug there was a fall in the erythrocyte sedimentation rate and a decrease in the serum mucoprotein. A study of synovial permeability in rabbits revealed that during administration of chlorpromazine the urinary excretion of phenolsulphonphthalein introduced into the talo-crural joints was slowed down, compared with that in rabbits not receiving the drug. There was some reduction in capillary permeability in four patients with degenerative arthritis and three with rheumatoid arthritis during chlorpromazine treatment. The effect of the drug on hyaluronidase activity *in vitro* and *in vivo* was also studied. The viscosity of a mucin emulsion was measured and compared with the viscosity of an equal quantity of the mucin emulsion after hyaluronidase or hyaluronidase and chlorpromazine had been added. Hyaluronidase activity *in vivo* was measured by noting the area of diffusion on indian ink with hyaluronidase or hyaluronidase and chlorpromazine added to it. The results *in vivo* and *in vitro* appeared to indicate that chlorpromazine has some antihyaluronidase action.

In view of this evidence of anti-rheumatic activity and of the known action of chlorpromazine on the nervous system, it was considered possible that the drug might be of value in the treatment of patients during the difficult period immediately following discontinuance of cortisone therapy. Chlorpromazine in a dosage of 150 to 250 mg. daily was given for a period varying from 10 to 20 days to fifteen patients who had been receiving cortisone; small doses of corticotrophic (ACTH) were also given. It was found that with this treatment the rebound syndrome which follows cessation of steroid therapy was avoided.

C. E. Quin.

Chloroquine Phosphate (Aralen) in the Long-term Treatment of Rheumatoid Arthritis. YOUNG, J. P. (1959). *Ann. intern. Med.*, **51**, 1159. 4 figs, 22 refs.

The author reports the results obtained with "aralen" (chloroquine phosphate) in the treatment of rheumatoid arthritis in fifty consecutive patients, 41 female and nine

male, seen in private practice. The average duration of the arthritis before treatment was 9 years. Classified according to the severity of the disease by the criteria of the American Rheumatism Association eighteen of the patients were in Stage I (no radiological destructive changes apparent), 23 in Stage II (slight, cartilage or bone destruction without joint deformity), eight in Stage III (cartilage and bone destruction with joint deformity), and one in Stage IV (bony or fibrous ankylosis). The initial dosage of chloroquine was 62 mg. three times weekly, but this was so well tolerated that later patients were given a starting dosage of 125 mg. three times weekly. At varying intervals, usually every 2 weeks, the dose was cautiously increased according to the patient's response. When a dose was reached that produced improvement, it was maintained indefinitely. The highest dosage, in a few cases only, was 500 mg. six times weekly. The treatment was continued for one year after all symptoms had been relieved, the period of continuous therapy varying from 17 to 36 months. Of eight patients who showed signs of mild toxicity all but two were able to continue with the treatment. Various additional therapeutic measures for the relief of symptoms included administration of salicylates and other analgesics, phenylbutazone, steroids for short periods, and the intra-articular injection of steroids in some cases.

Of the eighteen patients in Stage I, twelve (67 per cent.) went into complete remission and six (33 per cent.) showed major improvement. Of 23 in Stage II, nine (39 per cent.) remitted and thirteen (57 per cent.) showed major improvement.

The overall results were that, of the fifty patients, 44 (88 per cent.) showed major improvement or complete remission, all of these being initially graded Stage I or II. The six patients with poor response were initially graded Stage III or IV. Treatment with chloroquine was followed by a return to normal of the erythrocyte sedimentation rate and the haematocrit value in a much higher percentage of patients than has been observed in previous series treated with steroids, phenylbutazone, or aspirin.

[This study unfortunately does not conform to the requirements of a controlled therapeutic trial.]

Kenneth Stone.

Treatment of Rheumatoid Arthritis by Local Application of Intermittent Pressure. [In English.] LÖVGREN, O., and RASTGELDI, S. (1959). *Acta rheum. scand.*, **5**, 240. 3 figs, 19 refs.

It is pointed out that in rheumatoid arthritis fixation of joints merely causes muscular atrophy, while active and passive movements, which are desirable, increase pain. This pain is caused by unevenly distributed pressure acting on rheumatoid tissue; if such pressure could be evenly distributed there would be less likelihood of pain. The authors, at St. Erik's Hospital, Stockholm, have devised special apparatus for applying evenly distributed intermittent pressure to the hands, legs, and feet. It consists of inflatable rubber cushions attached to an air compressor which delivers intermittent pressure between 0 and 200 or 300 mm. Hg at a frequency of 40 to 60 beats a minute. Treatment for half an hour causes no discomfort. It is claimed that peri- and intra-articular oedema in rheumatoid arthritis is reduced and that in gouty arthritis uric acid excretion is significantly increased by this form of treatment.

The authors suggest that steroids and salicylates modify electrolyte and fluid exchange between the circulating plasma and interstitial fluid, and that a similar effect can be obtained by intermittent pressure therapy without the disadvantages associated with the use of drugs and hormones. *D. Preiskel.*

Correction and Prevention of Deformity in Rheumatoid Arthritis: Active Immobilization. KELLY, M. (1959). *Canad. med. Ass. J.*, **81**, 827. 6 figs, 14 refs.

From the Institute of Rheumatology, Melbourne, comes this practical article on the prevention of deformity of the wrist and knee in patients with rheumatoid arthritis. The author's thesis is that if these deformities are prevented so that the patient can continue to use his hands and to walk he is unlikely to become crippled.

Arthritis of the wrist may be responsible for swelling of the whole hand. The author advises fixing the wrist in a plaster cast, in the correct position, leaving the thumb and fingers free. Relief of pain in the fingers quickly follows immobilization of the wrist. After 3 weeks the plaster can be removed and thereafter a leather support is worn intermittently. To prevent flexion deformity of the knee the use of a cylindrical plaster cast, or a straight calliper with a band at the top instead of a ring, is advocated. The patient is encouraged to walk with the leg straight, and the importance of regular quadriceps exercises is stressed. It is suggested that if the knee is painful and swollen the appliance should be worn continuously for 3 weeks, after which it is left off for lengthening periods each day. In the author's experience immobilization of the wrist or the knee for 3 weeks seldom causes ankylosis provided the cartilage is intact; if the cartilage has disappeared "ankylosis is a happy result". The appliances used are well illustrated. *Kenneth Stone.*

Pleural and Pulmonary Complications of Rheumatoid Arthritis. HORLER, A. R., and THOMPSON, M. (1959). *Ann. intern. Med.*, **51**, 1179. 6 figs, bibl.

In this report from the Royal Victoria Infirmary, Newcastle upon Tyne, the authors present the case histories of ten patients with rheumatoid arthritis who developed pleural and pulmonary lesions, and exhaustively review recently acquired knowledge of this complication. Such lesions have been reported previously, in some instances with histological evidence, but nevertheless some authorities doubt whether they are specifically rheumatoid—if there is, in fact, such a condition as "rheumatoid lung".

The cases described occurred among 180 patients with rheumatoid arthritis seen at the hospital during the two years 1956 and 1957; nine were found to have or to have had a pleural effusion, two of these also having parenchymatous lung lesions, while one further patient showed changes in the lungs which were possibly rheumatoid in

nature. Causes other than rheumatoid arthritis were excluded so far as possible.

Of the nine patients with pleural effusion, eight were males. A review of the literature shows that pleural effusion complicating rheumatoid arthritis has occurred predominantly in men. The appearance of the effusion was accompanied by an acute febrile illness, in six cases this being a prodromal or inaugural event in the rheumatoid process. In one of these patients nodular lesions with the histological characters of the subcutaneous rheumatoid nodule were found in the lungs and pleura at necropsy, a finding similar to that previously reported by other workers. This patient, a coalminer with rheumatoid arthritis of 3 years' duration, developed a cough, breathlessness on exertion, and progressive loss of weight. Radiographs showed a right pleural effusion and nodular shadows in the right lung field, including a rounded mass suspected of being a carcinoma. At thoracotomy a thick-walled interlobar effusion was found, as well as a small nodule in the apical segment of the lower lobe, which was excised. Section of this nodule showed histological features identical with those of a subcutaneous rheumatoid nodule. Many references are given to previous reports of diffuse pulmonary lesions, these appearing radiographically as a diffuse mottling of the lung fields, and shown by biopsy examination to be a "chronic fibrosing pneumonitis". The authors' series included one such case which was associated with pleural effusion.

The term "honeycomb lung" has been applied to a radiographic appearance seen in a number of disorders, including tuberculosis, scleroderma, and rheumatoid arthritis. One case associated with rheumatoid arthritis is reported in this series. Pleural effusion is fairly common in systemic lupus erythematosus, but the authors give reasons for believing that their patients were suffering from rheumatoid arthritis and not from systemic lupus erythematosus, repeated search for L.E. cells giving a negative result in every case. Of the seven patients with pleural effusion alone, resolution occurred within a few months in six, after repeated thoracentesis; the seventh developed a symptomless encysted effusion. In the patients with diffuse fibrotic lesions the effusion recurred repeatedly for about a year and then became encysted. The patient with the nodular lung lesion required thoracentesis about once yearly, because of a slow recurrence of the effusion. The nodular lesion has, however, remained unchanged for more than 5 years.

Kenneth Stone.

On the Relationship between Divorce and Rheumatoid Arthritis. COBB, S., MILLER, M., and WIELAND, M. (1959). *Arthr. and Rheum.*, **2**, 414. 10 refs.

In the study here reported from the University of Pittsburgh the "interview index" for rheumatoid arthritis (R.A.) was considered to be positive if the interviewed subject admitted to ever having had arthritis or rheumatism, joint swelling, and morning stiffness or aching in the joints or muscles. Among a series of 499 persons who had filed divorce proceedings in the Courts of Allegheny County a positive R.A. index was recorded in eleven men and seventeen women. The R.A. positive-index rates were found to be higher than those in men and women (in a separate study) who had remained married. First marriages had lasted longer among the R.A. subjects with a positive index than among those with a negative index. These findings were more significant for men than for women and in the authors' opinion support the hypothesis that patients with rheumatoid arthritis are likely to exert a rigorous control over strong feelings of hostility, and so to delay divorce proceedings. Persons with poor education and low incomes showed a higher rate of positive R.A. indexes. In addition some significance is attached to the fact that 59 per cent. of women with a negative R.A. index and 82 per cent. of women with a positive R.A. index were in employment.

A. Garland.

Method of Drug Evaluation in Rheumatoid Arthritis: Results with Phenylbutazone, Oxphenylbutazone, Cortisone, and Prednisone. SMYTH, CHARLEY J. (1960). *Ann. N.Y. Acad. Sci.*, **86**, 292. 8 figs, 10 refs.

This study from the University of Colorado, Denver, is concerned with objective tests for the activity of rheumatoid arthritis. As the author points out, the need for these becomes increasingly apparent as new and more potent anti-inflammatory drugs are made available for clinical investigation.

The single blind technique was employed and a total of 58 patients were studied over 3 years.

Cortisone, phenylbutazone, and prednisone were each tested over a 5-month period, with a month on aspirin before and after each test period. Later oxyphenylbutazone was tested for periods of 1 month only.

At first the inflammatory indices of Lansbury and Haut were used, but these gave undue emphasis to large joints and were discarded. Eventually a method of measuring inflammation by recording pain, heat, redness, swelling, and fluid in pairs of joints was found satisfactory.

The functional indices used were:

(*a*) the distance between the styloid process of the radius and the acromio-clavicular joint;
(*b*) the grip test using a Beaumanometer;
(*c*) walking time over 25 feet.

The inflammatory and functional indices were analysed statistically and the author has devised a clear and comprehensive method of presenting the results.

These show clearly the advantages of both steroids and of phenylbutazone over aspirin. Not enough data was obtained for a clear opinion on oxyphenylbutazone.

[This is an excellent article and should be studied by those interested in objective measurements in rheumatoid arthritis.] *Oswald Savage.*

Active Immobilization for Arthritic Wrists and Knees. KELLY, M. (1960). *Arch. phys. Med.*, **41**, 152. 3 figs, no refs.

Active Immobilization for Recurrent or Chronic Polyarthritis. KELLY, M. (1960). *Med. J. Aust.*, **1**, 287. 8 figs, 9 refs.

Radiological Contribution to the Early Diagnosis and Classification of the Various Stages of Evolution of Rheumatoid Arthritis. (Contributo radiologico alla diagnosi precoce ed alla classificazione dei vari stadi evolutivi dell'artrite reumatoide.) BOCCACCIO, R., and CAPPONI, G. (1960). *Minerva med. (Torino)*, **51**, 760. 15 figs, 38 refs.

Systemic and Articular Indices as a Measure of the Activity and Progress of Rheumatoid Arthritis. LANSBURY, J. (1959). *Arch. interamer. Rheum.*, **2**, 628. 4 figs, 10 refs.

Significance of Housing and Dry Rot in the Aetiology of Rheumatoid Arthritis. (De betekenis van behuizing en houtrot voor het ontsaan van reumatoïde arthritis.) VAREKAMP, H. (1960). *Ned. T. Geneesk.*, **104**, 862. 5 figs, 16 refs.

Subluxation of the Knee-joint in Juvenile Rheumatoid Arthritis. (Die Subluxation der Kniegelenke bei pr.-chronischen Polyarthritis im Kindesalter.) STOER, G., and STOEBER, E. (1960). *Mschr. Kinderheilk.*, **108**, 246. 2 figs, 7 refs.

Anaemia and Disturbances of Iron Metabolism in Rheumatic Arthritis. (Anémie et troubles du métabolisme du fer au cours de la polyarthrite chronique rhumatismale.) RAVAULT, P.-P., VIGNON, G., LEJEUNE, E., and MAITREPIERRE, J. (1960). *Bull. Acad. nat. Med. (Paris)*, **144**, 182. 13 refs.

Hyperoestrogenismus and Rheumatoid Arthritis. KALLIOMÄKI, J. L., and RAURAMO, L. (1960). *Acta endocr. (Kbh.)*, **34**, 45. 7 refs.

Renal Function in Rheumatoid Arthritis. (Nyrefunktionsundersøgelser ved polyarthritis chronica.) SØRENSEN, A. W. S. (1960). *Ugeskr. Laeg.*, **122**, 364. 2 figs, 45 refs.

Steroid Excretion during Chloroquine Treatment for Rheumatoid Arthritis. (Steriodudskillelsen ved klorokinbehandlung af rheumatoid arthritis.) ERLENDSSON, F. (1960). *Ugeskr. Laeg.*, **122**, 629. 2 figs, 31 refs.

Rheumatoid Arthritis. Use of Antimalarial Agents in Treatment. STONE, JR., C. T. (1960). *Tex. St. J. Med.*, **56**, 98. 2 refs.

Treatment of Inflammatory Rheumatism with Antimalarials (Chloroquine and Hydroxychloroquine). (Le traitement des rhumatismes inflammatoires par les antimalariques [Chloroquine et Hydroxchloroquine].) KERUZORE, A., COSTE, F., and DELBARRE, F. (1960). *Sem. Hôp. Paris*, **36**, 999. 4 figs, 24 refs.

Disorders of Vision and Changes in the Eyes during the Treatment of Rheumatoid Arthritis with Quinoline Derivatives. (Über sehstörungen und augenveränderungen bei der chinolintherapie des primär chronischen gelenkrheumatismus.) MARX, R., BRECH, P., and MEISNER, T. (1960). *Klin. Wschr.*, **38**, 443. 3 figs, 14 refs.

Visual Prognosis in Still's Disease with Eye Involvement. SMILEY, W. K. (1960). *Proc. roy. Soc. Med.*, **53**, 196. 1 table, 4 refs.

Histamine Liberators in Chronic Articular Rheumatism. (I liberatori d'istamina nelle reumo-arthropatie croniche.) CERVINI, C., and CIOCCI, A. (1960). *Boll. Soc. ital. Biol. sper.*, **36**, 174. 12 refs.

(Osteo-Arthritis)

Osteo-Arthritis of the Spine. LICHTOR, A., LYMBEROPOULOS, P., and LICHTOR, J. (1959). *Amer. J. Surg.*, **98**, 683. 3 refs.

The lumbar spines of 54 subjects at *post mortem* examination were analysed to determine the relationship between the presence of osteophytes on the vertebral bodies, thinning of the intervertebral disk, and osteo-arthritis of the posterior apophyseal joint. The changes in each of the three anatomical sites were independent of the other two and developed from different causes.

From this study it is concluded that osteophytes on the vertebral bodies are not evidence of spinal arthritis.—[*Authors' summary.*]

Kinesitherapy in the Treatment of Osteo-Arthritis of the Hip. (Place de la kinésithérapie dans le traitement de la coxarthrose.) COSTE, F., LAURENT, F., and ILLOUZ, G. (1960). *Sem. Hôp. Paris*, **36**, 1008. 5 figs.

Surgical Treatment of Chronic Non-Specific Arthro-Synovitis of the Knee Joint. BONOLA, A. (1960). *Rheumatism*, **16**, 34. 3 figs, no refs.

Algodystrophies of the Knee. (Les algodystrophies du genou.) DE SÈZE, S., RENIER, J. C., and CARO, H. (1960). *Rev. Rhum.*, **27**, 9. 5 figs, 10 refs.

Clinical Aspects of Primary Aseptic Fragmentary Necroses of the Femoral Head in the Adult. (Aspects cliniques des nécroses parcellaires aseptiques primitives de la tête fémorale chez l'adulte.) SERRE, H., and SIMON, L. (1959). *Montpellier méd.*, **56**, 193. 6 figs.

(Spondylitis)

Arthritis of the Hip in Ankylosing Spondylitis. (Les coxites de la pelvi-spondylite rhumatismale.) DE SÈZE, S., LEQUESNE, M., and FORESTIER, F. (1959). *Rev. Rhum.*, **26**, 715. 9 figs, 7 refs.

Involvement of the hip in ankylosing spondylitis has been described by many workers. In this paper the authors analyse a series of 51 cases of ankylosing spondylitis in 25 of which unilateral and in 26 bilateral hip lesions were present. Only cases showing characteristic lesions of the sacro-iliac joints were included in the series. There were 34 males and seventeen females, their ages ranging from 20 to 50 years. In eleven cases, hip symptoms heralded the onset of the disease, and in three of them these symptoms persisted for several years,

but it could not be demonstrated that the hip lesion ever preceded sacro-iliac involvement. The knee-joints were affected in about half the cases.

Pain in the hip may be severe, moderate, minimal, or entirely absent, and may show acute exacerbations from time to time. Functional disability appears to be less than in rheumatoid arthritis, and there are other differentiating features. In ankylosing spondylitis synoviocapsulitis is common; in other words, the process is constrictive rather than destructive. At a later stage peripheral osteophytes develop. Characteristically, the radiological appearances lag behind the clinical signs, and even when the joint is immobile there is no true joint destruction, though osteoporosis of the femoral head and acetabulum is common in such cases. The acute stage may be treated with phenylbutazone, complete rest, and splintage in plaster. Various forms of arthroplasty may be considered in the chronic phase, but the results are often disappointing. *D. Preiskel.*

Spondylitis in Chronic Ulcerative Colitis. ZVAIFLER, N. J., and MARTEL, W. (1960). *Arthr. and Rheum.*, **3**, 76. 7 figs, 12 refs.

(Miscellaneous)

Treatment of Rheumatic and Degenerative Joint Disease with a Pyrazolone Derivative (Kr 132). (Trattamento delle artropatie reumatiche e degenerative con un derivato pirazolico (Kr 132).) BERARDI, G. C., and CHIAPUZZO, A. (1959). *Minerva med.* (*Torino*), **50**, 4145. 5 figs.

Pyrazolone derivatives, which have been used in the treatment of articular rheumatism since 1927, reduce the permeability of the serous membranes and the capillaries and encourage the reabsorption of inflammatory exudates, this anti-inflammatory action being accompanied by a marked antipyretic and analgesic effect. The chief disadvantage of these drugs hitherto has been the high incidence of side-effects, especially gastro-intestinal disturbances, even with soluble and injectable compounds. Kr 132 (Osadrin) is a new pyrazolone derivative which, it is claimed, can be administered in large doses with good therapeutic action and an almost total absence of side-effects. Chemically, this preparation consists of 1:4-diphenyl-3:5½-dioxypyrazolidine in the form of the diethylaminoethanolic salt, associated with aminophenazone, procaine, or *para*-aminobenzoic acid. The diethylaminoethanolic salt was used on account of its vasodilating action, making it particularly useful in the initial stages of rheumatic diseases, in which spastic constraction of the blood vessels has been observed.

In this paper from the Orthopaedic Clinic of the University of Genoa the authors report the treatment of 42 patients suffering from intensely painful osteoarthritis (37) and rheumatoid arthritis (5), a number of whom had previously been treated unsuccessfully with various other therapeutic agents, both medical and physical. Intramuscular injections of 5 ml. of a 30% solution of Osadrin were given daily for 15 to 20 days or until the disappearance of pain, followed by maintenance therapy given by mouth. Many of the patients continued the treatment at home after being discharged from hospital. Complete or partial relief of pain was obtained in 36 out of the 42 cases and was accompanied by improvement in mobility due to reduction in the contracture of the periarticular muscles. The best results were obtained in cases of severe pain of relatively recent origin.

The small group of cases of rheumatoid arthritis responded poorly, only three having a partial remission of pain. In five cases induration at the site of injection was observed which, however, yielded to local treatment in 2 to 3 days. One case of allergic eruption was observed which yielded promptly to anti-allergic treatment. No other side-effects were reported, and frequently repeated blood counts and liver function tests gave normal results. *Robert E. Lister.*

Adrenocortical Hormones in Combination with Pyrazolone Derivatives in the Treatment of Rheumatoid Arthritis in Children and Adults and of Ankylosing Spondylitis. (Nebennierenrindenhormone in Kombination mit Pyrazolon-Derivaten bei der Behandlung der chronischen Polyarthritis Jugendlicher und Erwachsener und der Spondylitis ankylopoetica.) KUIPERS, R. K. W. (1959). *Z. Rheumaforsch.*, **18**, 468. 1 fig., 13 refs.

At the Red Cross and N.E.B.O. Hospitals and the Juliana Children's Hospital, The Hague, the author has used phenylbutazone and other pyrazolone derivatives in the treatment of "several thousand patients suffering from juvenile polyarthritis, rheumatoid arthritis, and ankylosing spondylitis—excluding those suffering concomitantly from diseases of the stomach and gall-bladder, severe anaemia, and leucopenia. From this experience, he concludes that, provided the dosage is kept at its lowest useful level by means of serial estimations of the blood level, the pyrazolone drugs are of great therapeutic value in selected cases of these diseases. He has also found the adrenocortical steroids, especially prednisone, to be very effective in cases of rheumatoid arthritis and juvenile polyarthritis.

However, both types of drug have unwanted and sometimes dangerous side-effects even at the minimum effective dosage level, while with the steroids it is necessary to inject ACTH (corticotrophin) regularly in order to prevent adrenocortical atrophy. The author therefore tried to reduce the dose of both phenylbutazone and prednisone still further, especially for maintenance therapy over extended periods.

It was found that this was possible by giving both drugs simultaneously, the effective dose of each being then smaller than when either was given alone. The average optimum dosage was found to be 2·5 mg. prednisone and 100 mg. phenylbutazone three times daily; in some cases it could be reduced to 1·25 mg. of the former and 50 mg. of the latter four times daily. The two drugs could be given together in a sugar-coated tablet. Although some 60,000 such tablets in the lower dosage have now been administered, not a single case of severe gastric disturbance or leucopenia has been observed. Patients who developed skin

eruptions when given 200 to 400 mg. phenylbutazone daily were free of them when given 200 to 300 mg. combined with 5 to 7·5 mg. prednisone (four to six tablets) daily.

The results of the combined treatment in 300 cases of rheumatoid arthritis, eight of juvenile rheumatoid arthritis, and fifty of ankylosing spondylitis are reported. Before this treatment with prednisone-phenylbutazone tablets was initiated, all patients were observed for a period of 6 months or more, during which other remedies were given. The subsequent response to combined treatment, evaluated according to the standards of the American Rheumatological Association, was highly encouraging, only eight patients (all with rheumatoid arthritis) showing no improvement. Side-effects were few, one patient developing a mild gastric disturbance with negative radiological and chemical findings, and six others developing oliguria which yielded promptly to reduction of dosage. As no symptoms of adrenocortical atrophy were observed, ACTH injections were given only occasionally. The erythrocyte sedimentation rate and serum γ-globulin content reverted towards normal levels. A double-blind trial in which fifty cases of rheumatoid arthritis were treated with prednisone-phenylbutazone tablets and fifty with a placebo was also carried out and confirmed the effectiveness of the former.

Robert E. Lister.

Clinical Course of Arthritis associated with Ulcerative Colitis and Regional Ileitis. FORD, D. K., and VALLIS, D. G. (1959). *Arthr. and Rheum.*, **2**, 526. 16 refs.

The clinical course of arthritis complicating intestinal disease was studied in twenty patients (thirteen male and seven female) seen in three hospitals in Vancouver over a period of 9 years. In sixteen patients the arthritis was associated with ulcerative colitis and in four with regional ileitis. The response to the latex-fixation test, when performed, was negative.

In the cases of ulcerative colitis the arthritis was usually subacute, arising in a second or later attack of colitis rather than in the initial one. The knees and ankles were most commonly affected; hips, shoulders, elbows, hands, and spine were sometimes involved. The joint symptoms persisted for a month or two at a time and then tended to resolve completely, leaving little or no structural damage, but sometimes recurred when the colitis relapsed. Surgical treatment of the colitis led to permanent relief of the arthritis. Erythema nodosum was also seen in five patients, the lesions appearing at the same time as the arthritis in some instances.

In two of the four patients with regional ileitis, arthritis began before the intestinal disease was recognized, although it may well have been present in a clinically silent form. Again, the knees, elbows, and hands were involved episodically and the arthritis was relieved after surgical treatment of the ileitis. One patient had spondylitis with some residual spinal rigidity. *J. A. Cosh.*

Arthritis of Ulcerative Colitis. WRIGHT, V., and WATKINSON, G. (1959). *Medicine*, **38**, 243. 12 figs, bibl.

A consecutive series of 108 unselected patients (66 female) being treated in the wards or attending the follow-up clinic for colitis at the General Infirmary or St. James's Hospital, Leeds, were examined by a gastroenterologist and by a rheumatologist. The clinical features and course of both the colitis and the associated arthritis, where present, is described in detail.

In seventeen patients (15·7 per cent.), a specific type of arthritis was recognized which the authors designate as "colitic arthritis", 32 attacks having occurred in these seventeen patients. The onset of arthritic symptoms was acute in nine cases and insidious in the remainder. Only one joint was affected in nine patients. The knee was the joint most commonly affected initially, but the ankle was involved almost as frequently. In about two-thirds of the patients the initial attack finished within 6 weeks. In all but three patients a complete remission without residual disability occurred. Recurrent attacks most commonly involved the knees and the ankles and lasted less than 6 weeks in thirteen cases (69 per cent.). Recovery and restoration to normal function occurred in all patients. The Rose-Waaler agglutination test gave negative results in all seventeen patients. In the majority of the patients with colitic arthritis the colitis was chronic. A distinct relationship appeared to exist between recurrent exacerbations of the arthritis and the clinical activity of the colitis. Thus 27 of the 32 attacks of arthritis were accompanied by increased bowel symptoms, and in eighteen attacks the remission of bowel and joint symptoms occurred at the same time. The extent of the colonic inflammation was related to the frequency of joint symptoms. Colitic arthritis was significantly more common in patients with certain local complications, such as perianal suppuration and pseudopolyposis, though not with fistula formation or strictures. Similarly, a clear association appeared to exist between the systemic complications of colitis and attacks of arthritis, the latter occurring significantly more commonly in patients with ulceration of the mouth, skin lesions, and uveitis than in those without these complications. In the four patients in whom colectomy and ileostomy were performed, a prompt and prolonged remission of arthritic symptoms occurred.

In two of the patients with colitis, coincident rheumatoid arthritis was reported. This arthritis differed clinically and radiologically from the colitic arthritis, and the Rose-Waaler test gave positive results in both cases. The clinical features in a series of 95 patients with uncomplicated rheumatoid arthritis, in most of whom the Rose-Waaler reaction was positive are listed and compared with those described in the seventeen patients with colitic arthritis. Important differences are noted. The colitic arthritis was more commonly accompanied by marked constitutional disturbances than rheumatoid arthritis (53 to 39 per cent.), more often initially monarticular (53 to 39 per cent.), and much more frequently asymmetrical (65 to 5 per cent.). The exacerbations were of shorter duration in colitic than in rheumatoid arthritis. Complete recovery without residual disability was the rule in colitic arthritis (82 per cent.), but seldom occurred in rheumatoid arthritis (5 per cent.). Significant radiological changes developed in the majority of joints affected by rheumatoid arthritis, but with colitic

arthritis only minimal changes occurred, and these in a small percentage of patients. Both at the onset and during the course of the disease the joints of the upper limbs were affected three or four times more commonly in rheumatoid than in colitic arthritis, whereas arthritis of the knees was more common in the latter (82 to 60 per cent.).

The authors conclude from this comparison and from the serological findings that there are no grounds for regarding colitic arthritis as a variant of rheumatoid arthritis. Little evidence was found in this series of a relationship between colitic arthritis and ankylosing spondylitis.

[This paper merits studying in full and in conjunction with that of Bywaters and Ansell (*Ann. rheum. Dis.*, 1958, 77, 169).] *J. Warwick Buckler.*

Rheumatic Iridocyclitis. HAARR, M. (1960). *Acta ophthal. (Kbh.)*, **38**, 37. 16 refs.

Roentgen examination of the ilio-sacral joints of 252 male and 106 female patients with acute iridocyclitis showed Bechterew's disease in 103 males (40·9 per cent.) and eighteen females (17·3 per cent.). Of 81 male and 88 female patients with chronic iridocyclitis only one had signs of Bechterew's disease. Chronic polyarthritis was found in four males (1·6 per cent.) and three females (2·5 per cent.) with acute iridocyclitis, and in three males (3·7 per cent.) and three females (3·4 per cent.) with chronic iridocyclitis. Of 153 patients with Bechterew's disease, 32·6 per cent. had at least one attack of iridocyclitis, against 4·1 per cent. of 97 with chronic polyarthritis. Urogenital infection seems to be important as a causative factor in Bechterew's disease and acute iridocyclitis. *G. von Bahr.*

Uveitis, Arthritis, and Non-Specific Genital Infection. CATTERALL, R. D. (1960). *Brit. J. vener. Dis.*, **36**, 27. 1 ref.

The author describes an investigation of 222 patients suffering from uveitis: 142 were found to have chronic prostatitis, this lesion being more common among the cases of anterior uveitis than of posterior uveitis; 52 had Reiter's disease and a relationship was found with ankylosing spondylitis, atypical uveitis, and plantar fasciitis. No causative organism was found.

A. G. Cross.

Reiter's Syndrome. Report of Sixteen Cases, Eight of which followed Treatment for Gonorrhoea. STEINMETZ, P. R., and GREEN, J. P. (1959). *U.S. armed Forces med. J.*, **10**, 1185. 15 refs.

A general account with a detailed description of two cases. The characteristic features were in evidence and treatment with cortisone, prednisolone, or corticotrophin was more effective than that with salicylates. Penicillin and streptomycin were ineffective. Recovery ensued within 2-5 months. *M. H. T. Yuille.*

Surface Manifestations of Reiter's Disease in the Male. HANCOCK, J. A. H. (1960). *Brit. J. vener. Dis.*, **36**, 36. 13 figs, 4 refs.

Seventy-six cases were studied. Arthritis occurred in all but two. Eye lesions were present at some time in 45 per cent. of cases; conjunctivitis (37 per cent.) was the most common, involving specially the tarsal conjunctiva at the lateral angle. Anterior uveitis occurred in 8 per cent., and in some of these cases frequent recurrences were noted. Corneal involvement did not occur in this series. The other manifestations described are in the mouth (10 per cent.), on the skin (7·8 per cent.; keratoderma blennorrhagica typically on the soles of the feet), and on the penis (26 per cent.; balanitis circinate). *J. D. Abrams.*

Virus Aetiology of Epidemic Exanthem and Polyarthritis. SHOPE, R. E., and ANDERSON, S. G. (1960). *Med. J. Aust.*, **1**, 156. 17 refs.

Disk Syndrome

Lumbosacral Radiculography with Methiodal in Rheumatology. (La Radiculographie lombo-sacrée au méthiodal en rhumatologie.) SERRE, H., TEMPLE, J.-P., and JANICOT, J.-Y. (1959). *Montpellier méd.*, **56**, 153. 14 figs, 1 ref.

Diskogenic Disease, Backache, and Connective Tissue Function. VERNON, S. (1960). *J. Amer. Geriat. Soc.*, **8**, 195. 14 refs.

Conservative Management of "Low Back Syndrome". KESTLER, O. (1960). *J. Amer. med. Ass.*, **172**, 2039. 1 ref.

Gout

Renal Excretion of Uric Acid in Patients with Gout and in Non-gouty Subjects. NUGENT, C. A., and TYLER, F. H. (1959). 4 figs, 30 refs.

At the University of Utah College of Medicine, Salt Lake City, renal excretion of uric acid in gout was studied in six patients with the disease and seven healthy subjects, renal function tests being carried out on seven occasions in the former group and on ten occasions in the latter. The values for inulin and uric acid clearances, the proportion of filtered uric acid excreted, and the rate of uric acid excretion were similar in the two groups. A high-purine diet or 4 g. ribonucleic acid was given daily for 3 to 5 days to the controls in order to increase the plasma uric acid concentration and the filtered uric acid loads to the range found in patients with gout. Under these conditions the subjects without gout reabsorbed a smaller proportion of their filtered uric acid than did the patients with gout and the uric acid clearance and uric acid excretion rate were well above the levels observed in the latter group.

It is concluded that abnormal renal excretion of uric acid is one important cause of hyperuricaemia in some patients with gout. The results of the present investigation do not lend support to the view that overproduction of uric acid is the sole cause of hyperuricaemia in gout.

G. W. Csonka.

Gout in the Female. (La gota en la mujer.) ROTÉS-QUEROL, F., and RODRÍGUEZ CASTRO, A. (1959). *Rev. esp. Reum.*, **8**, 75. 4 figs, 14 refs.

Of 2,922 patients attending the Rheumatological Service of the Barcelona Faculty of Medicine, 118 had gout, of whom 17 were women. Diagnoses were based on the clinical picture and history of recurrent acute arthritis; serum urate estimations (4·5 to 5 mg. per 100 ml. in two, 5 to 6 mg. per 100 ml. in nine, 6 to 7 mg. per 100 ml. in three, and more than 7 mg. per 100 ml. in two cases) were regarded as providing supporting evidence only. One patient had tophi and two renal stones, while six out of the nine patients whose blood pressure was recorded had hypertension (over 150 mm. Hg systolic). [Other details of cardiac and renal status are not given.] Two patients also had evidence of rheumatoid arthritis, one with a positive Rose-Waaler reaction and radiographs showing typical erosions. Ten patients were menopausal or post-menopausal, two had never menstruated, and five were menstruating regularly; however, of these last, in only one did menstruation occur for a normal time and at normal intervals. Five of twelve married patients were barren.

The typical female patient with gout was plethoric, energetic, and somewhat virilized. The distribution and nature of the gouty arthritis did not differ from that observed in men. *Allan St. J. Dixon.*

Gout in Buenos Aires. (La gota que se observa en Buenos Aires.) MORENO, A. R. (1959). *Arch. argent. Reum.*, **22**, 91. 19 refs.

Pararheumatic (Collagen) Diseases

Systemic Lupus Erythematosus after "Idiopathic" Thrombocytopenic Purpura: a Review. RABINOWITZ, Y., and DAMESHEK, W. (1960). *Ann. intern. Med.*, **52**, 1. Bibl.

In this paper from the New England Center Hospital, Boston, the authors report the results of a re-examination of 44 out of 51 consecutive cases of idiopathic thrombocytopenic purpura in which splenectomy was performed between 1949 and 1955. In eight cases there was considered to be "definite" evidence of systemic lupus erythematosus (S.L.E.), such as discoid skin lesions, a positive reaction to the L.E.-cell test or histological lesions in the spleen or kidneys. In two cases S.L.E. was considered "probable", because arthritis or nephritis had developed or there was a positive reaction to the Coombs test. Non-specific evidence of systemic disease other than purpura was found in six cases which were regarded as "possible" cases of S.L.E. All the patients in these sixteen cases were females.

Of fourteen cases of "definite" S.L.E. following splenectomy for thrombocytopenic purpura (including the eight in the present series, four in which splenectomy was performed before 1949, and two operated on at other hospitals), three showed discoid skin lesions before splenectomy and five after the operation. In six there was a positive reaction to the L.E.-cell test after splenectomy, but in all such cases there was other evidence to support the diagnosis of S.L.E. In five of these fourteen cases thrombocytopenic purpura recurred after splenectomy, this relapse rate being similar to that in cases without evidence of S.L.E. In two cases splenectomy appeared to exacerbate S.L.E. *M. Wilkinson.*

Serum Proteins in Systemic Lupus Erythematosus. REES, E. G., and WILKINSON, M. (1959). *Brit. med. J.*, **2**, 795. 3 figs, 14 refs.

The author's report from St. Bartholomew's Hospital Medical School, London, the result of a study of the serum protein pattern in 31 patients with confirmed systemic lupus erythematosus and in a control group of twelve healthy young adults by means of paper electrophoresis. They found a statistically significant rise in the average total protein level and in the γ-globulin fraction and a fall in the albumin and α_2- and β-globulin fractions in the eighteen patients with untreated systemic lupus erythematosus who had not persistent proteinuria, the γ-globulin level being notably high in seventeen of these patients. The authors consider that the diagnosis of systemic lupus erythematosus is unlikely if the γ-globulin level is normal in the absence of a considerable degree of proteinuria.

In seven patients with persistent proteinuria, the serum albumin level was even lower, but the increases in the levels of the α_2- and γ-globulin fractions were less marked than in the uncomplicated cases. The protein in the urine of one patient consisted predominantly of albumin. The serum protein pattern slowly returned towards normal during steroid therapy. The authors interpret the observed rise in the γ-globulin fraction as "the biochemical expression of a raised antibody level, much of which may be auto-antibody". The other changes observed are regarded as non-specific effects of severe disease. *G. L. Asherson.*

Reaction of the Lupus Erythematosus (L.E.) Cell Factor with Deoxyribonucleoprotein of the Cell Nucleus. HOLMAN, H., and DEICHER, H. R. (1959). *J. clin. Invest.*, **38**, 2059. 4 figs, 27 refs.

In this very complicated study of the L.E.-cell factor, undertaken at the Rockefeller Institute, New York, in an attempt to identify the nuclear component on which the factor acts, prepared pellets of nucleoprotein of calf thymus gland were found to absorb protein (shown by means of fluorescein-labelled antibody to be gamma globulin) from L.E. sera, but not from other sera. After absorption the L.E. sera lost their ability to induce L.E.-cell formation. Digestion of the nucleoprotein-L.E.-cell factor complex with deoxyribonuclease released deoxyribonucleic acid (DNA) and some gamma globulin; the latter had no L.E.-cell factor potency, but did fix complement with isolated DNA. When the residue remaining after digestion was eluted at 56° C. in isotonic saline solution more gamma globulin was released and this proved to be largely L.E.-cell factor.

Nucleoprotein from which either DNA or histone had been removed showed little capacity to absorb L.E.-cell

factor, but when the residue from nucleoprotein extracted with acid to remove the histone was recombined with the extracted histone there was considerable restoration of L.E.-cell factor activity. However, combination of this same residue with protamine instead of histone gave a product without L.E.-cell factor activity. The combination between nucleoprotein and L.E.-cell factor was inhibited in the presence of histone, protamine, or mepacrine. Immunoelectrophoretic studies using L.E. cell factor and antisera against the two main molecular constituents of normal gamma globulin (which have sedimentation rates of 7S and 19S respectively) showed that the L.E.-cell factor reacted with antisera against normal human 7S gamma globulin. This antiserum abolished the ability of L.E. sera to induce L.E.-cell formation. Finally, complete absorption of the L.E.-cell factor from a serum by isolated cell nuclei caused only a small reduction in the amount of gamma globulin present.

The authors interpret these results as indicating that the L.E.-cell factor reacts with deoxyribonucleoprotein and that it requires both DNA and histone for the reaction. This finding, similar to that of other reported studies, seems to separate the L.E.-cell factor from the factor which reacts with DNA and complement, and which is found in only a minority of L.E. sera. The authors suggest that the L.E.-cell factor is probably only one of a number of antinuclear antibodies developed in systemic lupus erythematosus. *M. Wilkinson.*

Study in the Existence of L.E. Cells in Active Rheumatoid Arthritis. LENOCH, F., VOJTISEK, O., and MARSIKOVÁ, L. (1959). *Arch. interamer. Rheum.*, **2**, 456. 8 tab., bibl.

The authors, at the Rheumatic Diseases Research Institute, Prague, examined 208 women and 82 men with rheumatoid arthritis (R.A.) (Stages 2, 3, and 4 of the American Rheumatism Association classification), for lupus erythematosus (L.E.) cells. They adopted the criteria of Heller and Zimmerman in the interpretation of positive tests; *i.e.* they divided their findings into:

Strictly L.E. cells (completely amorphous and ill-defined inclusion body), found in six patients;
Type B cells (inclusion body with defined edge and traces of cromatin net), found in 21 cases;
Type A cells (smaller inclusion body with well-defined cromatin net) found in 45 cases.

One of the six cases with strict L.E. cells had marked proteinuria, implying possible systemic L.E., but the other patients did not differ from those with Type A or Type B cells. Other methods of detecting L.E. cells were tried in a proportion of cases with fewer positive results. The authors conclude that L.E. cells do not appear more frequently in R.A. than in other diseases which they reviewed.

[Technical factors such as time taken to view each blood film are of paramount importance in the assessment of the results of L.E. cell tests. Such details are not given nor is there mention of the authors' own experience of the strict interpretation of tests in the laboratory diagnosis of clinically undisputed systemic L.E. In the reviewers' opinion the authors' conclusion cannot be drawn from the evidence presented.]

A. St. J. Dixon.

Hereditary Hypergammaglobulinaemia and Systemic Lupus Erythematosus. I. Clinical and Electrophoretic Studies. [In English.] LARSSON, O., and LEONHARDT, T. (1959). *Acta med. scand.*, **165**, 371. 4 figs, 39 refs.

The authors, working at Hässleholm and Malmö General Hospitals, Sweden, have studied two families in which there was a striking incidence of systemic lupus erythematosus and hypergammaglobulinaemia. In the first family three cases of systemic lupus erythematosus and one of hypergammaglobulinaemia (serum γ-globulin level 3·78 g. per 100 ml.) occurred in a sibship of fourteen, while in the second there were two cases of systemic lupus erythematosus, one of hypergammaglobulinaemia (serum γ-globulin level 1·70 g. per 100 ml.) in a uniovular twin sister of one of these patients, and one of rheumatoid arthritis in a sibship of five; a distant relative of this family also suffered from systemic lupus erythematosus.

The diagnosis of systemic lupus erythematosus was based on a strongly suggestive history; in two cases L.E. cells could not be demonstrated. In regard to serum γ-globulin level, which was measured by paper electrophoresis, the mean value for seventy marriage partners in these families was 1·01 g. per 100 ml. (S.D. 0·18). In the first family the mean serum γ-globulin level for 112 members was significantly raised (1·12 g. per 100 ml. S.D. 0·23), this rise being most marked in the sibs of the patients with systemic lupus erythematosus (1·32 g. per 100 ml., S.D. 0·16), and present though less marked in their nephews and nieces (1·14 g. per 100 ml.). It was also noted that first, but not second, cousins showed raised values; in the second family the increase in serum γ-globulin levels was less marked. These differences could not be attributed to differences in age, sex, or state of health between the families and the controls. The other serum protein fractions were normal. There was a positive correlation between the size of the serum γ-globulin fraction and the erythrocyte sedimentation rate (E.S.R.), though in some subjects with hypergammaglobulinaemia the E.S.R. was normal.

The authors emphasize the significance of the finding of three cases of systemic lupus erythematosus in a sibship of fourteen. Between 1954 and 1958 there were admitted to Malmö General Hospital, which serves a population of about 210,000, only thirty cases of systemic lupus erythematosus. In the absence of evidence that systemic lupus erythematosus is an infectious illness they consider that the "demonstration of familial occurrence argues for hereditary factors". As hypergammaglobulinaemia occurred in these same families and was also apparently genetically determined, it seems probable that a common aetiological factor, possibly genetic, underlies both systemic lupus erythematosus and hypergammaglobulinaemia. The occurrence of rheumatoid arthritis in one sib of the second family and of a positive

Rose-Waaler reaction in the sib with hypergammaglobulinaemia in the first family suggests that rheumatoid arthritis is also related to these conditions. The histories of the identical twins, one having systemic lupus erythematosus and the other hypergammaglobulinaemia, were compatible with the view that recurrent infections and/or drug therapy are important in provoking the development of frank systemic lupus erythematosus. Relevant findings reported in the literature are cited.

[The special importance of this and the following paper lies in the evidence put forward, which suggests that systemic lupus erythematosus, with its associated autoantibody formation, occurs in patients who for genetic reasons are good producers of circulating antibody.]

G. L. Asherson.

II. Serological Studies. [In English.] LEONHARDT, T. (1959). *Acta med. scand.*, **165**, 395. 2 figs, 19 refs.

The author has investigated the serological reactions in some 100 members of a family with a high incidence of hypergammaglobulinaemia and in which three cases of systemic lupus erythematosus had occurred in a sibship of fourteen. A control group of about thirty members was provided by the marriage partners of the family.

A raised anticomplement titre was found in only two subjects—that is, two of the three patients with systemic lupus erythematosus. The Wassermann, Kahn, and Kline reactions were negative in all subjects. The rheumatoid arthritis serum factor, as determined by the Rose-Waaler reaction, was raised in all three sibs with systemic lupus erythematosus and in a fourth sib with essential hypergammaglobulinaemia (titre 1:1,024). One relative with rheumatoid arthritis had a raised titre (1:64) and five others (cousins) had borderline values (1:32); however, three of the controls also showed elevated figures.

In tests for the rheumatoid factor by its ability to agglutinate cells coated with incomplete anti-Rh serum, four of the relatives gave a positive reaction and six relatives and one control subject a weakly positive reaction. The antistreptolysin titre was raised in two of the three patients with systemic lupus erythematosus and in the fourth sib with hypergammaglobulinaemia. This titre was shown to be raised more often in the sibs (in four out of ten and in nephews and nieces (nineteen out of 31) of the patients than in the controls (twelve out of 37) and patients' second cousins (eight out of 24). The author attributed this significant difference in part to a hereditary tendency to increased antibody production. The antistaphylolysin titre was not significantly raised in any of the subjects. However, nine of the twelve sibs tested showed iso-agglutinin titres greater than 1·16, as compared with six out of 26 of the controls. The first and second cousins of the patients with systemic lupus erythematosus, but not the nephews and nieces, also showed significantly raised iso-agglutinin titres.

There was no correlation between the serum γ-globulin level and the antistreptolysin or iso-agglutinin titre, nor were serum antibody and α-globulin levels related to the ABO or Rh blood groups or the Gm serum groups of Glubb. The L.E.-cell test was positive in two of the three patients with systemic lupus erythematosus, but in none of the 21 other members of the family with a raised serum γ-globulin level. No circulating anticoagulant was detected in eleven of these subjects.

The author considers that the finding of a strongly positive Rose-Waaler reaction in the sib with essential hypergammaglobulinaemia as well as in the three sibs with systemic lupus erythematosus confirms the previous conclusion that hypergammaglobulinaemia, rheumatoid arthritis, and systemic lupus erythematosus are related conditions.

G. L. Asherson.

Retinopathy in Acute Disseminated Lupus Erythematosus. [In Czech.] OTRADOVEC, J., and VLADYKOVÁ, J. (1959). *Sborn. lék.*, **61**, 228. 22 refs.

Description of a case in a boy aged 14 with typical changes in the fundi. In microscopic examination of the eye, enlarged degenerated nerve fibres were found, corresponding to a white disc in ophthalmic examination.

M. Klíma.

Pathology of Mikulicz-Sjögren Disease in Relation to Disseminated Lupus Erythematosus. Review of the Autopsy Findings and Presentation of a Case. BAIN, G. O. (1960). *Canad. med. Ass. J.*, **82**, 143. 5 figs, 39 refs.

Mikulicz's disease and Sjögren's syndrome may be regarded as varying clinical expressions of the same underlying disease process. The specific lesion found in the lacrimal gland may occur as an isolated mass in a major salivary gland or as multiple lesions in the major and minor salivary glands. It may be seen with xerostomia, arthritis, and other conditions. The lesions in these glands are remarkably similar to the *post mortem* findings in systemic lupus erythematosus. There are morphological similarities between the changes in Mikulicz-Sjögren's disease amd in the thyroid lesion of Hashimoto's disease.

C. McCulloch.

Lupus Erythematosus Nephritis. I. Clinical and Anatomical Study of Fourteen Cases. (Les lupoérythémato-néphrites. I. Étude clinique et anatomique de quatorze observations.) CROSNIER, J., SLAMA, R., and DE MONTERA, H. (1960). *Presse méd.*, **68**, 148.

The authors, working at the Hôpital Necker, Paris, studied fourteen cases of systemic lupus erythmatosus (S.L.E.) which presented to them because of renal involvement. All the patients were female, twelve ranging in age from 15 to 38. The presenting renal feature was almost invariably proteinuria, often about 5 mg. per minute, sometimes less marked but increasing with time. The proteinuria was always persistent. Haematuria of some degree could always be detected by an Addis count, and macroscopic haematuria occurred in one patient. Eleven patients had oedema, but only three had frank hypertension. The interval between the onset of S.L.E. and proteinuria was very variable, but once proteinuria appeared the prognosis worsened and renal function test results deteriorated over 2 to

12 months. Indeed, four patients died within a month and only in two cases were the results of renal function tests normal after 3 years. The clinical features of lupus nephritis were not distinctive, but the rapid progression to uraemia of the nephrotic syndrome in a young woman in the absence of hypertension is considered to be suggestive. In three patients the first manifestation of S.L.E. was renal. In four other cases a careful history revealed past evidence of S.L.E., such as bouts of fever and arthralgia. In five cases the presence of the renal lesion facilitated the diagnosis of an obscure illness and in only two cases did the renal lesion occur in known cases of S.L.E. Characteristic fundal changes occurred in two patients.

Anaemia and an increased erythrocyte sedimentation rate were common. Five patients had frank leucopenia, but this sometimes disappeared when the patient became uraemic. L.E. cells were found at some stage in twelve patients and were persistent in nine. Five out of nine patients had antibodies against deoxyribonucleic acid. Serum electrophoresis showed an increased γ-globulin content in three of the eleven cases with the nephrotic syndrome and a considerable depression of the β_1A-globulin level and an elevation of that of β_2A-globulin not seen in other cases of the nephrotic syndrome. These changes in the β-globulin levels persisted even when the L.E.-cell and serological tests had become negative during treatment with steroids.

The renal histology was studied in biopsy or necropsy specimens from eleven patients. In five the changes were focal and involved only some of the glomeruli. In the remainder they were general. Thickening of the basement membrane was a constant finding, and in all but one patient was irregular in distribution. The wire-loop appearance was seen only in seven patients. Fibrinoid necrosis of the basement membrane occurred in seven patients. The material was positive to the periodic-acid-Schiff test, was destroyed by trysin, and was distinct from collagen and hyaline. Fibrinoid thrombi were seen in the glomerular capillaries in six cases. Haematoxylin bodies occurred in only one case. Vascular changes were minimal in the eight biopsy specimens, but were seen in the four necropsy specimens.

The authors were unable to show any correlation between the renal histology and the results of renal function tests, but consider that there was a general relationship between the degree of proteinuria and the basement-membrane changes. *G. L. Asherson.*

Renal Involvement in the Schönlein-Henoch Syndrome. (L'atteinte rénale au cours du syndrome de Schönlein-Henoch.) BOUISSOU, H., DUPONT, H. G., and RÉGNIER, C. (1959). *Arch. franç. Pédiat.*, **16**, 890. 5 figs, 39 refs.

A survey of the literature on the subject of renal involvement in the Henoch-Schönlein syndrome, the incidence of which varies from 24 to 54 per cent., left the authors in considerable doubt about both the pathological nature of the kidney involvement and its prognosis. They therefore studied 22 children who were being treated for Henoch-Schönlein purpura at the Children's Clinic of the University of Toulouse. Eight children developed nephritis, and needle biopsy of the kidney was performed ten times on five of these, three consecutive biopsies being performed in two cases and two in another. In addition a needle biopsy was performed on a child without detectable renal involvement. [The result was normal. A doubtfully justifiable procedure.] The clinical features of the nephritis corresponded well to those already well known from the work of others. Histologically, the lesions were confined to the glomerulus, and at the first examination were identical to those in acute glomerulo-nephritis (based on examination of 6 to 21 glomeruli in each biopsy specimen). Later, sclerotic changes appeared or the kidney returned to normal.

[This is a very long and repetitive paper. A vast number of conclusions are drawn from insufficient material and are therefore largely on a speculative basis. Although the authors set out to improve on the many unsatisfactory papers already available on this subject, they have merely succeeded in adding one more to the list. The only novelty is the serial needle biopsy of the kidney, which gave the expected results.] *John Lorber.*

Mechanism of Lidase Action in the Treatment of Patients with Scleroderma. [In Russian.] RAHMANOV, V. A., and HMEL'NICKIJ, R. H. (1959). *Vestn. Derm. Vener.*, **33**, 3. 3 figs, 9 refs.

Most authorities consider that in the collagen diseases there is a breakdown of the hyaluronidase system, which in its turn influences the metabolic processes in the intercellular connective tissue. There may be splitting of the collagen into its components, and on biochemical analysis the protein and polysaccharide ingredients of the altered collagen of the hyaluronic and chondroitinsulphuric acid types can be demonstrated. Hyaluronidase is the specific enzyme which depolymerizes these molecular combinations. A number of single cases of successful treatment of scleroderma with hyaluronidase have been described in the literature. These descriptions and the authors' own experiments have shown that there is decreased tissue permeability in patients with scleroderma, and this led to the present clinical trial of "lidase", a Soviet hyaluronidase-like preparation, which was carried out in 34 cases.

After treatment, sixteen of the cases in which there was diffuse scleroderma and sclerodactyly showed a general improvement, this including softening of the skin, depigmentation, disappearance of trophic ulcers, decrease in the feeling of cold, and an increased range of movement in the large joints. Resolution of the sclerodermal process was also observed. Lidase had no effect on very advanced cases, but improvement was noted in eighteen patients with localized scleroderma. There were no complications and the only side-effects observed were increased urination and two cases of mild urticaria. Microscopical examination after treatment showed that there was increased vascular and tissue permeability.

[The lidase appears to have been given by injection.] *N. Hopewell.*

Involvement of the Brain in Generalized Periarteritis Nodosa. (Die Gehirnbeteiligung bei generalisierter Panarteriitis nodosa.) MARTIN, H., and NOETZEL, H. (1959). *Beitr. path. Anat.*, **121**, 347. 9 figs, bibl.

At the Pathological Institute of the University of Freiburg the authors have found involvement of the central nervous system in eleven out of fourteen consecutive cases of periarteritis nodosa coming to necropsy, the brain alone being involved in nine cases, the brain and spinal cord in one, and the spinal cord alone in one.

The medium-sized and small arteries showed the typical picture of necrosis, cellular infiltration, and occasional scarring, while the larger arterial branches showed only intimal proliferation. The fibrinoid changes seen in arterioles and in the smallest arteries were regarded as non-specific. In the leptomeninges, the lesions of periarteritis in the smaller vessels were observed in three cases, and intimal proliferation was recorded in seven. The vessels affected in the brain showed no particular distribution, typical changes being noted in both intracerebral and intramedullary vessels; one case showed scarring and an aneurysm which had given rise to haemorrhage. Examination of the spinal cord in eight cases revealed arteritis in one. The vascular lesions in the brain had resulted in macroscopic scarring in three cases and haemorrhage in a further two; petechial haemorrhages were commonly seen. Histologically, necrosis, glial proliferation, and occasional demyelination were found. All eleven cases in which the central nervous system was involved also showed vascular lesions in the peripheral nerves. *G. Loewi.*

Ophthalmological Manifestations of Periarteritis Nodosa. (Manifestations ophtalmologiques de la périartérite noueuse.) MOREAU, P. G. (1959). *Presse méd.*, **67**, 735.

Periarteritis nodosa may lead to three types of ocular manifestations:

(1) Signs due to the ocular localization of the disease (choroidal lesions similar to tubercles, narrowing of the retinal arteries, scleritis, and oculomotor disorders);
(2) signs due to systemic hypertension and nephritis (malignant hypertensive retinitis);
(3) Dysoric nodules. *S. Vallon.*

Polyarteritis Nodosa. A Case with Ocular Lesions, Nodes, and Livedo racemosa. (Polyarteritis nudosa. A propósito de un caso con lesiones oculares iniciales, nódulos y livedo racemosa.) BALIÑA, L. M., NOUSSITOU, F., and MUZZIO, J. C. (1959). *Arch. Oftal. B. Aires*, **33**, 103. 3 figs.

A 12-year-old boy with polyarteritis nodosa is described, whose first symptom was a bilateral iridocyclitis with cataract and complete loss of vision. On the skin he had livedo racemosa, many nodes, and a generalized oedema. [*Author's summary.*]

Systemic Lupus Erythematosus: a Review of Certain Recent Developments in the Study of this Disease. HOLMAN, H. (1960). *J. Pediat.*, **56**, 109. 2 figs, bibl.

Plasma Coagulation Defect in Systemic Lupus Erythematosus arising from Hypoprothrombinaemia combined with Antiprothrombinase Activity. RAPAPORT, S. I., AMES, S. B., and DUVALL, B. J. (1960). *Blood*, **15**, 212. 30 refs.

Synthetic Antimalarial Drug Therapy in Lupus Erythematosus and Polymorphous Light Eruptions. EPSTEIN, J. H. (1960). *Calif. Med.*, **92**, 135. 6 refs.

Clinical Relationships of Lung Changes in Disseminated Lupus Erythematosus. (Die klinischen Beziehungen der Lungenveränderungen bei Lupus erythematosus disseminatus.) LEÖVEY, A., and BERKOVITS, L. (1960). *Wien. Z. inn. Med.*, **41**, 152. 4 figs, 33 refs.

Two Types of L.E.-Cell Factor shown by Induced L.E.-Cell Phenomenon in Dogs. BENCZE, G., LAKATOS, L., AND LUDÁNYI, M. (1960). *Brit. med. J.*, **1**, 1707. 2 refs.

Psychosis and Systemic Lupus Erythematosus. FESSEL, W. J., and SOLOMON, G. F. (1960). *Calif. Med.*, **92**, 266. 53 refs.

Roentgen Manifestations of Collagen Diseases. NICE, C. M. (1960). *J. Louisiana med. Soc.*, **112**, 119. 4 figs, 41 refs.

Disorders of Movement, Suppression of Reflexes, and Electrical Findings in Sclerodermatous and Myositic Processes. (Bewegungsstörungen, Reflexverhalten, elektrische Befunde bei sklerodermischen und myositischen Prozessen.) KIRCHHOF, J. K. J., and KLINGMÜLLER, G. (1960). *Nervenarzt*, **31**, 162. 7 figs, bibl.

General Pathology

Serum Proteins in Health and Disease. Filter Paper Electrophoresis. OGRYZLO, M. A., MACLACHLAN, M., DAUPHINEE, J. A., and FLETCHER, A. A. (1959). *Amer. J. Med.*, **27**, 596. 18 figs, bibl.

In this report from the Sunnybrook (D.V.R.) Hospital and the University of Toronto, the results of paper electrophoresis of specimens of serum from 100 normal adults are compared with those of specimens from patients with rheumatoid arthritis and other collagen diseases, liver disease, colitis, kidney disease, leukaemia, multiple myeloma, and agammaglobulinaemia. It was noteworthy that in the 100 normal subjects the results were all very much alike and that determinations showing a significant deviation from normal values were not in general consistent with continued good health. On the other hand, the authors emphasize that normal electrophoretic patterns may be observed in a proportion of cases of most of the diseases which were included in the present study. The pathological sera came from a large number of subjects. The group of rheumatic and collagen diseases consisted of 150 cases of rheumatoid arthritis, 36 of systemic and seven of discoid lupus

erythematosus, twenty of scleroderma, eight of dermatomyositis, six of polyarteritis, fifteen of rheumatic fever, 35 of "undifferentiated collagen disease", 49 of gout, 113 of spondylitis, and eight of Reiter's syndrome. There were also nine cases of sarcoidosis, 52 of liver disease, four of gastro-intestinal disease, 53 of renal disease, 34 of leukaemia or lymphoma, fifty of multiple myeloma, and three of agammaglobulinaemia.

In general, the accepted characteristics of the electrophoretic patterns in the various conditions examined were confirmed, although it is stressed that not all patients in each category will necessarily show a typically abnormal serum protein pattern. Serum electrophoresis is perhaps particularly useful in the differentiation of cases of the nephrotic syndrome resulting from glomerulonephritis, in which the γ-globulin fraction is reduced and the α_2-globulin fraction is increased, from cases of the nephrotic syndrome associated with systemic lupus erythematosus and of other diseases with renal involvement, in which the γ-globulin fraction is normal and the α_2-globulin fraction is either also normal or a little increased. Serum electrophoresis is also, of course, of the greatest diagnostic value in myelomatosis and agammaglobulinaemia.

[It is not possible to summarize the authors' detailed observations, for which the original paper should be consulted.] *H. Lehmann.*

Rheumatoid Arthritis and Hereditary Serum Groups. (Reumatoïde arthritis en erfelijke serum-groepen.) VAN DE WIEL, T. W. M. (1959). *Ned. T. Geneesk.*, **103**, 2314. 3 figs, 24 refs.

At the Central Laboratory of the Transfusion Service of the Netherlands Red Cross, Amsterdam, sera from patients with rheumatoid arthritis ("rheumatoid" sera) were tested for agglutinating power against human erythrocytes sensitized with the corresponding antiserum. Positive agglutination was obtained with some "rheumatoid" sera against seventeen out of 48 human antisera examined (anti-D, K, c, A). Of 118 rheumatoid sera, fifty were negative to the Rose-Waaler test and gave no positive agglutination reaction; 68 were Rose-Waaler positive and 33 of these gave positive agglutination reactions. The Rose-Waaler reaction became negative in these sera after absorption with denatured γ globulin (that is, by removal of the rheumatoid factor). The Gm factor was determined, using D cells sensitized with an incomplete anti-D antiserum. It was present in 69 of the 118 rheumatoid sera, in 81 of 140 sera from close relatives of these patients, and in 296 of 500 sera from blood donors. These findings suggest that the Gm factor is not concerned with the development of the rheumatoid factor in rheumatoid arthritis. The Gm factor was present in all of 725 sera from natives of New Guinea, suggesting that the distribution of the Gm^a gene is related to race rather than to disease.

Rabbit serum inhibited the agglutination by a "rheumatoid" serum of Group O, Rh-positive human erythrocytes sensitized with rabbit antiserum, but had little inhibitory effect when the cells were sensitized with anti-D antiserum. *M. Lubran.*

Laboratory Investigations in the Diagnosis of the Difficult and Early Cases of Rheumatoid Arthritis. COKE, H. (1959). *Arch. interamer. Rheum.*, **2**, 391. 39 refs.

A number of tests suitable to routine clinical laboratories are discussed in the light of their application to the diagnosis of rheumatoid arthritis in a series of cases attending as ambulant out-patients.

The agglutination tests are demonstrated as of the most value, the sheep-cell haemagglutination test being the most sensitive and advantageous. 84·3 per cent. correct results were obtained in a series of 1,000 cases, 72·4 per cent. being positive in 633 cases of clinical rheumatoid arthritis. Lower levels of positivity were noted in early cases and in those in therapeutic remission. Sex differences are noted and analysed towards substantiating a degenerative endocrine polyarthritis of the climacteric as a syndrome which is not the true rheumatoid arthritis. An 83 per cent. correlation with a latex particle inhibition test is recorded. Significant biochemical abnormalities in gamma-globulin, alpha- seromucoid trypsin, and chymotrypsin inhibitors, and in the polarographic Brdicka waves are related to their use as additional confirmatory aids in the diagnosis of rheumatoid arthritis.

Discussion as to the necessity for agreement of more closely defined sub-groups of the rheumatoid disease process and similar but non-rheumatoid syndrome, is recommended until a more specifically defined aetiology is obtainable.—[*Author's summary.*]

New Agglutination Reaction in the Diagnosis of Rheumatic Diseases: the Hyland RA-test. ELDON, K., JARLØV, N. V., and STRANDBERG, B. (1959). *Dan. med. Bull.*, **6**, 286. 8 refs.

This communication from two Copenhagen County hospitals describes the technique and results of the "Hyland RA" test for the "rheumatoid factor" in 45 cases of confirmed rheumatoid arthritis and in 91 cases of "para-rheumatic" diseases. Of the 45 cases of rheumatoid arthritis, 41 (91 per cent.) gave a positive result, compared with only 5·5 per cent. of the other series. The three cases of ankylosing spondylitis tested also gave a positive reaction. The results of the Hyland RA test compared favourably with those of such tests as determination of the antistreptolysin titre, antistreptococcal hyaluronidase, and streptococcal agglutination titre. [No comparisons were made with other more sensitive tests for the rheumatoid factor.] The results of electrophoretic examination of the sera and of estimations of the haemoglobin level and the erythrocyte sedimentation rate are also reported. *D. M. Weir.*

Role of Spinal Fluid Transaminase Determination in the Differential Diagnosis of Low Back Pain. STEVENS, J. D., HUMOLLER, F. L., and MAJKA, F. A. (1959). *Bull. Los Angeles Neurol. Soc.*, **24**, 220. 4 refs.

The value of the glutamic oxalacetic transaminase (G.O.T.) level in the cerebrospinal fluid (C.S.F.) in the differential diagnosis of low back pain was studied at the Veterans Administration Hospital, Sepulveda, California.

The authors state that on the basis of experience in 238 cases, they consider that the normal G.O.T. level in the C.S.F. is 10 units or less. In four patients with osteo-arthritis of the spine and in eleven with back sprain the level was normal; of seventeen patients with prolapsed disk, however, the G.O.T. level was below 10 units in only six. The average value in these patients was 13·4 units, the level in one being 38·2 units. The authors consider that the raised G.O.T. level in the C.S.F. may be a useful diagnostic aid in cases of prolapsed disk.

K. C. Robinson.

Reactions in the Latex-Fixation Test for Rheumatoid Arthritis with Serum of Syphilitic Individuals. BLOOMFIELD, N. (1960). *J. Lab. clin. Med.*, **55**, 73. 6 refs.

Out of 232 sera from individuals with sero-positive syphilis tested in the laboratories of the New York State Department of Health, fifteen reacted with the latex-fixation test (Hyland RA test). There was no evidence of rheumatoid arthritis in fourteen, but the 15th had a mild asymptomatic hypertrophic arthritis of both hands. As a control, the RA test was carried out on 200 sera from presumably non-syphilitic individuals, none of which gave a positive reaction. These findings suggest that syphilis may cause false positive reactions in latex-fixation tests for rheumatoid arthritis, but no firm conclusions should be drawn until such cases have been followed for several years to rule out impending clinical arthritic disease. An additional case illustrates this point—a woman with neurosyphilis gave positive serum reactions for the rheumatoid factor in the absence of a history or evidence of rheumatoid arthritis, but a year later clinical and radiological evidence of rheumatoid arthritis was present.

G. W. Csonka.

Latex-Fixation Reaction in Non-rheumatic Diseases. DRESNER, E., and TROMBLY, P. (1959). *New Engl. J. Med.*, **261**, 981. 3 figs, 32 refs.

The paper from the Lemuel Shattuck Hospital and Harvard Medical School, Boston, reports the authors' experience in examining sera from 404 cases of non-rheumatic disease for the purpose of assessing the specificity of the agglutinating factor to the rheumatic disease process. Agglutination reactions were performed by both the coated latex particle agglutination technique and the inhibition phenomenon of Ziff. Both whole serum and the separated euglobulin fraction were used and all sera were treated previously by heat at 56° C. for 30 minutes. [The titre constituting a positive reaction is not specified.] Of 140 normal control subjects, seven gave positive euglobulin inhibition reactions, however, which later became negative after the subsidence of mild viral infections. Tests on 137 sera from patients with rheumatoid arthritis demonstrated the higher degree of sensitivity of the euglobulin inhibition procedure, which gave a positive reaction in 96 per cent. of cases compared with 62 per cent. with the standard serum test.

Among the 404 cases of non-arthritic disease a positive reaction to the euglobulin inhibition test was obtained in 31·4 per cent. Of these, 90 per cent. (28·4 per cent. of the total) fell within the three major disease groups which are noted for giving positive reactions—chronic hepatic diseases, viral infections, and syphilis. Figures are given to support the value of the test as a measure of activity in hepatocellular disease, which is shown to have no relation to the presence of jaundice. Agglutinating activity was present in 83 per cent. of 35 cases of active viral infection, remaining positive for 2 to 22 weeks. Of nineteen cases of syphilis, eighteen gave a positive reaction in the euglobulin inhibition test, but only two with whole serum. Agglutinating activity was present in only five out of twenty cases of hyperglobulinaemia.

In a lengthy discussion the authors relate the occurrence of positive latex-fixation and other reactions in both rheumatic and non-rheumatic diseases to the presence of factors with common physical properties [but not, apparently, with any consideration of the concept that the agglutination phenomenon might be essentially due to the absence of an inhibitor substance].

Harry Coke.

Mastic-Fixation Reaction in Rheumatoid Arthritis. A Modified and Simplified Latex-Fixation Test. (De mastix-fixatiereactie bij reumatoïde arthritis. Een gewijzigde en vereenvoudigde latex-fixatieproef.) PIT, A. A. (1959). *Ned. T. Geneesk.*, **103**, 2310. 10 refs.

A modification of the latex-fixation test for rheumatoid arthritis is described in this paper from the University of Amsterdam in which a stable suspension of mastic in borate or glycine buffer at *p*H 8·2 is treated with human γ globulin and added to varying dilutions of the serum to be tested. The degree of agglutination is read after 22 hours at room temperature, titres of 1:20 or higher being regarded as positive. The test was more sensitive with glycine than with borate buffer, the former giving 97 positive results out of 105 sera from patients with definite rheumatoid arthritis, the latter 72 out of 103. The results of the glycine-mastic test agreed with those of the latex-fixation test in 209 out of 244 cases (88 per cent.) and with the Rose-Waaler test in 72 out of 85 cases (85 per cent.). A few false positive results were obtained with both borate and glycine buffer with sera from patients with diseases other than rheumatoid arthritis, the highest proportion being in cases of disseminated lupus erythematosus (eight positive out of eleven sera). There were no positive reactions with sera from normal subjects. Tests on sera from 34 patients with a high serum γ-globulin level but without rheumatoid arthritis gave a positive reaction in eleven cases.

M. Lubran.

Comparison of Methods for the Estimation of Serum Cholesterol and Values in Random Samples of Populations in the 55-64 Age Group. MORRIS, T. G. (1959). *J. clin. Path.*, **12**, 518. 3 figs, 18 refs.

Increasing mortality from coronary disease has focused attention on the cholesterol level of blood as one of the many factors connected with the aetiology of the disease. Many methods have been proposed for the difficult estimation of blood cholesterol levels, and six of these methods, namely, those of Pearson and others (*Analyt. Chem.*, 1953, **25**, 813), Zlatkis and others (*J. Lab.*

clin. Med., 1953, **41**, 486), Trinder (*Analyst*, 1952, **77**, 321), Sackett (*J. biol. Chem.*, 1925, **64**, 203), Anderson and Keys (K.5) (*Clin. Chem.*, 1956, **2**, 145), and Sperry and Webb (*J. biol. Chem.*, 1950, **187**, 97), have been compared by carrying out determinations in triplicate by each method on ten sera.

The method of Trinder was the most reproducible, and those of Anderson and Keys (K.5) and Sperry and Webb the next most reproducible. Sackett's method was the least reproducible. Mean levels obtained with the methods of Sperry and Webb and Anderson and Keys (K.5) did not differ; the mean by Trinder's method was 4·2 per cent. higher and the mean by Sackett's method 7·3 per cent. higher than these two. The methods of Pearson and others and Zlatkis and others gave means 8·8 and 51·8 per cent. higher respectively. The methods of Trinder and Anderson and Keys (K.5) are the most suitable for routine use, and Trinder's method involves less manipulation and is quicker.

Cholesterol levels in random samples of populations in different areas, in the age group 55 to 64, were determined by Trinder's method to gain basic information for comparative purposes.—[*From the author's summary.*]

Intravenous Congo Red Test: a Description of Some Unrecognized Fallacies with Suggested Improvements. MORGAN, W. K. C., and MULES, J. E. (1960). *Amer. J. med. Sci.*, **239**, 61. 2 figs, 10 refs.

In this paper from the University of Maryland School of Medicine, Baltimore, certain fallacies and inaccuracies in the current method of measuring amyloidosis by the intravenous Congo red test are discussed. The Congo red test is based on the fact that amyloid tissue removes the dye from serum. Its accuracy rests on the assumption that the dye is completely free to pass to amyloid tissue in the body; but evidence has been obtained *in vitro* by Larsen (*Ann. rheum. Dis.*, 1958, **17**, 240) that the serum proteins have a certain binding capacity for the dye. A further assumption is that all forms of secondary amyloid take up the dye with equal avidity, although it is known that the amyloid found in primary amyloidosis does not take up the dye so rapidly as that in secondary amyloidosis. Other sources of error are technical. The dye is eluted from serum with acetone, which precipitates protein. Sometimes some of the dye is adsorbed by the protein and on other occasions the supernatant is cloudy. A major improvement is claimed by using sodium sulphate solution instead of acetone for precipitation.

From the results of tests by this improved technique on forty patients with arthritic and other diseases, the authors conclude that increased absorption of Congo red is probably no more frequent in rheumatoid arthritis without amyloidosis than in other conditions such as serum sickness and hepatic cirrhosis. *H. Lehmann.*

Cellular Origin of Rheumatoid Factor. MELLORS, R. C., HEIMER, R., CORCOS, J., and KORNGOLD, L. (1959). *J. exp. Med.*, **110**, 875. 24 figs, 12 refs.

Serological tests for rheumatoid arthritis basically involve reactions between the rheumatoid factor in the patient's serum and γ globulin of human or animal origin. Rheumatoid factor itself is in the serum macroglobulin (19S) fraction and readily reacts with polydisperse molecular aggregates of γ globulin (with sedimentation constants between 7 and 40) to form insoluble precipitates. These facts have been used in the work described in this paper from the Hospital for Special Surgery, New York, to study the cellular origin of rheumatoid factor. Fluorescein-labelled human γ globulin was aggregated by heating to 62° C. for 10 minutes, and the aggregated globulin recovered after precipitation by the addition of 40 per cent. by volume of 2·18 M sodium sulphate solution. This reagent, together with fluorescein-labelled goat anti-human γ globulin antibody (against 7S and/or 19S globulin) and fluorescein-labelled rabbit antihuman macroglobulin antibody (rendered specific for 19S globulin by absorption with 7S globulin) was used to stain frozen sections of tissue. The tissues examined were from ten patients with active classic rheumatoid arthritis and included synovial tissues, lymph nodes, subcutaneous nodules, and biopsy specimens of skin and muscle. Tissues from control subjects without rheumatoid arthritis were also examined.

In synovial membranes from the patients with rheumatoid arthritis the aggregated γ globulin stained only the cytoplasm (including Russell bodies) of cells of the plasma-cell series. The cytoplasm of similar cells similarly distributed was also stained by the fluorescent antibody to 19S globulin, but this staining was inhibited by pre-treatment of the section with unlabelled aggregated human γ globulin. It was concluded from these two observations that the positive cytoplasmic staining was due to the presence of rheumatoid factor in these cells. They constituted only a small minority of the mononuclear inflammatory cells present, but no rheumatoid factor was seen in any other type of cell in synovial tissue. In lymph nodes from one case the presence of rheumatoid factor and of 19S γ globulin was demonstrated by similar methods in some of the plasma cells in the medullary cords and in the "intrinsic" cells of about 10 per cent. of the germinal centres. In contrast, in about 80 per cent. of the germinal centres the cytoplasm of the "intrinsic" cells gave positive staining for 7S and/or 19 S globulin with goat anti-human γ-globulin conjugate (see Ortega and Mellors, *J. exp. Med.*, 1957, **106**, 627). In material from rheumatoid nodules (two patients) plasma cells containing rheumatoid factor were occasionally seen in paravascular foci in the outer inflammatory zone only. Control tissue from normal individuals and patients with non-rheumatoid arthritis were uniformly negative for rheumatoid factor.

The authors point out that all the patients with rheumatoid arthritis whose tissues were examined gave a high-titre latex-fixation reaction. Their results argue that rheumatoid factor is not only contained in, but is produced by, plasma cells and germinal-centre cells, and they consider that it is significant with regard to the underlying mechanism of the disease that actively inflamed synovial membrane contains plasma cells forming and liberating rheumatoid factor. *E. J. Holborow.*

Urinary Excretion of Thiamine, Riboflavin, Nicotinic Acid, and Pantothenic Acid in Patients with Rheumatoid Arthritis. KALLIOMÄKI, J. L., LAINE, V. A. I., and MARKKANEN, T. K. (1960). *Acta med. scand.*, **166**, 275. 11 refs.

Urinary and Blood Amino Acids in Rheumatoid Arthritis. I. KULONEN, M., and KULONEN, E. (1960). *Scand. J. clin. Lab. Invest.*, **12**, 84. 3 figs, 53 refs.

"Rheumatoid" Serologic Reactions in Experimental Animals. II. Bentonite Flocculation Test in Rats with Experimental Arthritis. LERNER, E. M., II, BLOCH, K. J., and WILLIAMS, R. R., JR. (1960). *Arthr. and Rheum.*, **3**, 26. 5 figs, 24 refs.

ACTH, Cortisone, and Other Steroids

Injection of Concentrated Prednisolone Trimethylacetate intra-articularly in Rheumatoid Arthritis. CARDOE, N. (1959). *Proc. roy. Soc. Med.*, **52**, 1109. 1 fig., 1 ref.

It has been observed that in rheumatoid arthritis injections of hydrocortisone into the finger-joints are much more effective than similar injections into larger joints. The present author attributes this to the higher concentration of the steroid which results from injection into the smaller joint. He has therefore given intra-articular injections of prednisolone trimethylacetate in a concentration of 200 mg. in 3 ml. to 22 patients with rheumatoid arthritis, a total of eighty injections being given into 25 different knee-joints. Since all the patients had previously received intra-articular injections of hydrocortisone up to a dosage of 100 mg. per injection, it was possible to compare the effects of the two preparations. The results were assessed partly on subjective and partly on objective evidence. There was a favourable response in nineteen cases. In five the results were so good that only a single injection was necessary. Effusions cleared in some cases after one or more injections without aspiration of fluid, but in most cases aspiration was necessary. The average duration of relief after injection was 5 to 7 weeks, as against 2 weeks after hydrocortisone. Complications and side-effects were negligible. The author considers that the technique can be relied upon to give much better and more lasting results than intra-articular injection of hydrocortisone in the usual low concentration. *William Hughes.*

Effect of Triamcinolone on Psoriatic Arthritis—a Two-Year Study. HOLLANDER, J. L., BROWN, JR., E. M., JESSAR, R. A., UDELL, L., COOPERBAND, S., and SMUKLER, N. M. (1959). *Arthr. and Rheum.*, **2**, 513. 5 figs, 5 refs.

Triamcinolone was given in the treatment of psoriatic arthritis of long standing in seventeen patients at the Hospital of the University of Pennsylvania, Philadelphia. For several months previously eleven of the seventeen had received prednisone, and in these triamcinolone was substituted in equivalent dosage; in general the dosage ranged from 6 to 16 mg. a day. In twelve of the seventeen there was major improvement or complete clearing of the psoriasis within a few weeks of the start of treatment. In fifteen the arthritis was better controlled with triamcinolone than with other steroids. Over a 2-year period partial relapse of the psoriasis occurred in most patients; however, triamcinolone appeared to control the skin lesions better than other steroids, because a change to the latter was followed by deterioration in the psoriasis. At the end of 2 years fourteen patients were still taking triamcinolone.

Side-effects, which were frequent, included moon face, hirsutism, facial flushing, and muscle weakness in a few patients in the early stages. Later on, peptic ulcer developed in one patient, but this healed in spite of continued administration of triamcinolone; another patient suffered collapse of a vertebral body from osteoporosis; and in a third renal failure from chronic nephritis developed.

It is concluded that triamcinolone shows promise in the treatment of patients in whom psoriasis and arthritis are severe and intractable enough "to justify the calculated risk and expense of any prolonged steroid therapy". *J. A. Cosh.*

Clinical and Metabolic Effects of Aldosterone Antagonism. SLATER, J. D. H., MOXHAM, A., HURTER, R., and NABARRO, J. D. N. (1959). *Lancet*, **2**, 931. 5 figs, 22 refs.

It is now well known that most patients who are accumulating oedematous fluid excrete considerable amounts of aldosterone in the urine, and the excessive production of aldosterone may well be a factor in the formation of oedema. A new series of synthetic steroids characterized by a spirolactone group on the 17th carbon atom of the *cyclo*pentenophenanthrene ring have been reported to antagonize the renal effects of aldosterone and deoxycortone in the adrenalectomized rat and dog.

In the present study, carried out at the Middlesex Hospital, London, the possibility of reducing oedema by inhibiting aldosterone production with one of these steroid spirolactones, SC 8109, was investigated in five patients with severe fluid retention. The spirolactone was first shown to inhibit the sodium retention and potassium loss caused by the administration of aldosterone in two adrenalectomized dogs. Of the five patients, two with the nephrotic syndrome and one with cirrhosis of the liver lost sodium and retained potassium when treated with spirolactone. However, two patients in cardiac failure did not respond well to spirolactone alone, but one of them showed a good diuresis when chlorothiazide was combined with the spirolactone. The findings of other workers have suggested that the spirolactones act by antagonizing the peripheral responses to aldosterone, but measurement of the aldosterone secretion rates in two of the patients in this study and of the urinary *p*H-1-extractable aldosterone in two others did not support this suggestion. *P. A. Nasmyth.*

Abnormal Response of Oedematous Patients to Aldosterone or Deoxycortone. NELSON, D. H., and AUGUST, J. T. (1959). *Lancet*, **2**, 883. 4 figs, 12 refs.

In this paper from the Peter Bent Brigham Hospital (Harvard Medical School), Boston, the authors report in

some detail the results of administering aldosterone in daily doses of 3 to 6 mg. and deoxycortone in daily doses of 15 to 30 mg. to four oedematous patients whose oedema was due to hepatic cirrhosis, congestive cardiac failure, nephrosis, and hypoproteinaemia respectively. In all four cases sodium retention became almost absolute, the 24-hour urinary excretion of sodium falling to between 0·3 and 2·9 mEq., compared with corresponding values of 12 and 31 mEq. in two normal controls. No effect on urinary potassium excretion was noted, although there was increased potassium excretion in the controls. These studies demonstrate the absence of secondary "escape" from the renal sodium-retaining effects of these steroids, the completeness of sodium reabsorption, and the failure to excrete increased amounts of potassium, thus confirming that in oedematous patients the response to aldosterone is abnormal . *H. F. Reichenfeld.*

Reliability of Some Adrenal Function Tests. COPE, C. L., and BLACK, E. G. (1959). *Brit. med. J.*, **2**, 1117. 8 figs, 11 refs.

The activity of the adrenal cortex is usually assessed by estimating the level of excretion of certain adrenocortical metabolites in the urine, such as 17-ketosteroids and 17-ketogenic steroids. Although some useful information can be obtained by such estimations performed before and after stimulation or inhibition of the adrenal gland, the difficulties involved in the separation of these metabolites and in the interpretation of the results are well known. One of the major products of the adrenal cortex is cortisol. The usefulness of estimation of the plasma cortisol level was explored by Bayliss (*Brit. med. J.*, 1955, **1**, 495), but was shown to be unreliable because of its natural wide fluctuations and diurnal rhythm. The urinary cortisol content, however, can be estimated with reasonable accuracy and with no great difficulty by a method described by Cope and Hurlock (*Clin. Sci.*, 1954, **13**, 69) and the main cortisol metabolites, tetrahydrocortisone and tetrahydrocortisol, can also be measured in the urine, although the latter technique is more time-consuming. The value of these tests is assessed in this paper from the Postgraduate Medical School of London.

The urinary excretion of various steroids, cortisone, cortisol, tetrahydrocortisone, tetrahydrocortisol, 17-ketosteroids, and 17-ketogenic steroids was measured in twelve cases of Cushing's syndrome. Urinary cortisol was found to be far the most sensitive index of adrenal hyperactivity. Moreover, inhibition of hyperactivity by administration of a synthetic steroid such as prednisone was reflected most markedly in the urinary cortisol level. Since normal subjects have been found to show urinary cortisol values near the lower limit of detection possible by the method, assay of cortisol in the urine is unsatisfactory for diagnosis of hypoadrenalism. However, a sensitive measure of this condition is provided by estimating urinary tetrahydrocortisol and tetrahydrocortisone excretion, values as low as 5 per cent. of normal being detectable.

The cortisol production rate, assessed by the use of radioactive cortisol, did not correlate well with steroid excretion, but was reflected more accurately by the 17-ketogenic steroid output than that of other urinary steroids. The authors conclude that adrenal function tests should be specially selected for the problem under investigation, 17-ketogenic steroid assay probably being the best general test for routine clinical use.

Nancy Gough.

State of Blood Potassium and Blood Sodium during Treatment with Triamcinolone. (Comportamento della potassiaemia e della sodienia in corso di terapia con triamcinolone.) MASTURZO, A., SCALA, E., BATTARRA, P., LUISO, E., and SAVINO, A. (1959). *Rec. Progr. Med.*, **27**, 47.

The authors, writing from the Rheumatic Centre of the Sovreign Order of Malta and the Pausilipon Hospital Laboratory of Chemistry and Microscopy, Naples, state that a disturbance of water-electrolyte balance may offset the benefits of cortisone treatment. This effect was studied in sixty patients treated with Triamcinolone. The authors concentrated on the blood levels of sodium and potassium because of their greater diagnostic and therapeutic importance.

The oedema noted in 28 per cent. of cases was slight and readily controlled. Some disturbance of the Na/K ratio occurred in 23 per cent. of cases but was marked in only seven. Changes in blood sodium were negligible. Potassium never deviated by more than 11 or 12 per cent. from the normal or pre-treatment levels. These disturbances of blood sodium and blood potassium never occurred before treatment.

A cortisone derivative that does not displace the Na/K ratio beyond safe limits is of great significance. Oedema did occur in 28 per cent. of cases, but was always slight and readily corrected.

In 15 per cent. of cases, the electrocardiogram was that of hypopotassaemia, but there was never any serious impairment of atrioventricular conduction.

The authors conclude that triamcinolone is the treatment of choice in the rheumatic diseases.

A. C. F. Green.

Radiological Bone Changes in Cushing's Syndrome and Steroid Therapy. MURRAY, R. O. (1960). *Brit. J. Radiol.*, **33**, 1. 10 figs, 49 refs.

In this paper from the Institute of Orthopaedics and the Royal National Orthopaedic Hospital, London, the author presents a detailed review of the bone changes in Cushing's disease and also the iatrogenic skeletal changes produced by adrenocortical steroid therapy, these being illustrated by ten case histories. The principal radiological feature of Cushing's disease is osteoporosis, particularly of the axial skeleton, with characteristic marginal condensation in the upper and lower surfaces of the vertebral bodies. Pathological fractures are common and are characterized by pseudo-callus formation, producing a "cotton-wool" appearance; they may be seen in the spine, femoral neck, ribs, and pelvis and are usually relatively painless, apart from root compression by a spinal compression fracture. Retardation of skeletal development occurs in children.

The author stresses the fact that although very similar skeletal changes can be produced by treatment with 50 to 100 mg. cortisone daily (or the equivalent dosage of a similar steroid) for 6 months or more, in practice such changes are not a common complication of steroid therapy, except in the case of intra-articular injections which can produce changes indistinguishable from neurarthropathy. In giving prolonged steroid therapy the problem of the uncontrolled spread of infection in the absence of inflammation and other symptoms must also be considered. *D. E. Fletcher.*

Pituitary Tumors in Patients with Cushing's Syndrome. SALASSA, R. M., KEARNS, T. P., KERNOHAN, J. W., SPRAGUE, R. G., and MACCARTY, C. S. (1959). *J. clin. Endocr.*, **19**, 1523. 7 figs, 16 refs.

In a series of 156 patients, a tumour of the adrenal cortex was found in 34; the remaining 122 (including those with glands of normal size) had adrenal cortical hyperplasia. Twelve of the latter, but none of the former, had radiological evidence of a pituitary tumour either before or after adrenalectomy. These twelve cases are described and two more are mentioned in an addendum.

There were nine women and three men; their ages ranged from 21 to 60. Cushing's syndrome was severe in eight, moderate in one, and mild in three, and had been present for 4 months to 10 years. Evidence of a pituitary tumour was present before adrenalectomy in nine cases and appeared 5 years after adrenalectomy in the other three, with a recurrence of Cushing's syndrome in two of them. Five patients had visual field defects, four had cranial nerve palsies, and six had neither. The visual symptoms often progressed rapidly.

The authors point out that the occurrence of a pituitary tumour in these cases could hardly be coincidental or the result of excessive adrenal cortical secretion; they discuss its significance and treatment. *G. C. R. Morris.*

Diseases and Problems from the Borderlines of Internal Medicine. V. Blue Sclerotics as a Symptom of Alarm. (Erkrankungen und Probleme aus den Grenzgebieten der Inneren Medizin. V. Blaue Skleren als Alarmsymptom.) JESSERER, H. (1959). *Med. Klin.*, **54**, 2218.

Idiopathic osteo-psathyrosis is thoroughly discussed. The author warns against corticosteroids or electroshock in such cases, as they can cause fractures.

W. Leydhecker.

Should Steroids be used in Juvenile Rheumatoid Arthritis· EDSTRÖM, G. (1959). *Acta rheum. scand.*, **5**, 263. 6 figs, 21 refs.

Clinical Experience with ACTH and Adrenocortical Steroids in 96 Cases of Rheumatoid Arthritis. SOLEM, J. H., and RÖMCKE, O. (1959). *Acta rheum. scand.*, **5**, 275. 2 figs, 7 refs.

Intramuscular Prednisolone Acetate in Rheumatology. (Acetato de prednisolona intramuscular en reumatologia.) NEBÓ, F. (1960). *Rev. argent. Reum.*, **24**, 284. 15 refs.

Clinical Results of the Use of Dexamethasone Acetate in Rheumatology. (Resultados clínicos do emprêgo do acetato de dexametasona em reumatologia.) BORBA, P., GOMES, G., and ESTANISLAU DA SILVA, J. (1960). *Hospital* (*Rio de J.*), **57**, 501. 8 refs.

Dexamethasone in Rheumatology (Preliminary Results). (L'hexadécadrol en rhumatologie [premiers résultats].) SERRE, H., and BARJON, M.-CL. (1959). *Montpellier méd.*, **56**, 183. 14 refs.

Therapeutic Trials of Dexamethasone Acetate in Rheumatology. (Essais thérapeutiques de l'acétate de dexamethasone en rhumatologie.) VIGNON, G., PERRIN-FAYOLLE, M., BOUVIER, M., and RONDELET, J. (1960). *Lyon méd.*, **203**, 859. 1 fig., 19 refs.

Other General Subjects

Treatment with Pyrazole Derivatives and Muscle Relaxants in Rheumatic Diseases. (Terapia pirazolica e miorilassante nelle malattie reumatiche.) REIFF, G. (1960). *Policlinico, Sez. prat.*, **67**, 86. 2 figs, 16 refs.

Muscular hypertonus in the rheumatic diseases is due to the reaction of the muscles to painful stimuli which, if more pronounced and sustained, may result in contracture. The latter condition is reversible, but if allowed to persist beyond a certain period it results in permanent atrophy and sclerosis. The therapeutic use of muscle relaxants in combination with anti-rheumatic drugs has therefore been studied by various workers in the hope that it would tend to diminish muscular spasms and contractures or even eliminate them completely. Among the substances tested clinically, mephenesin has given the most satisfactory results. Compared with curare its paralysing action is more gradual and the margin between active and toxic dosage is more ample for equal duration of action. Mephenesin diminishes cortical and medullary reflex excitability and prevents the passage of abnormal impulses across the reflex arc.

At the Institute of Rheumatology of the University of Rome, favourable results in preliminary trials of mephenesin have led to the use of "Myopyrin", a preparation containing two pyrazole compounds, mephenesin, and an antihistaminic ("Allantan"). Although "numerous" patients have been treated with this compound, only 37 have been sufficiently followed up to provide statistical material. Of these, fourteen were suffering from osteo-arthritis, mainly vertebral, six from "acute lumbalgia", four from "acute lumbalgia" complicated by sciatica, seven from rheumatoid arthritis, five from scapulo-humeral periarthritis, and one from rheumatic fever. Outstanding symptoms in all cases were spontaneous pain and pain provoked by movement, muscular spasm, functional limitation, and in some cases postural abnormality. No other anti-rheumatic drugs were given, but treatment included dietetic measures (with vitamins and anti-anaemic drugs) and exercise alternating with rest in bed. The dosage of Myopyrin was six tablets

(each containing 0·75 g. mephenesin) daily for 5 to 7 days, followed by four tablets daily for approximately a fortnight. In some cases the night doses were given in the form of suppositories. Pronounced improvement of all symptoms in various degrees was apparent within 3 to 10 days. Only one patient was refractory to treatment, though even in this case muscular spasm was reduced. The erythrocyte sedimentation rate was markedly reduced in most cases. *Robert E. Lister.*

Consistent Differences in Individual Reactions to Drugs and Dummies. JOYCE, C. R. B. (1959). *Brit. J. Pharmacol.*, **14**, 512. 1 fig., 29 refs.

The tendency of some individuals to report changes of physical and mental state after taking pharmacologically inert substances has been investigated experimentally. In a class of healthy medical students, those individuals who reported symptoms and those who did not made significantly different scores on a number of behavioural tests. The likely reactions of the members of a second class (containing none of the previous participants) to dummies were then predicted from their scores on the same tests, some of which were found to be much more efficient predictors than would have been expected by chance. Some implications for further research and for clinical medicine are discussed.—[*Author's summary*]

Digital Circulation in Raynaud's Disease. MENDLOWITZ, M., and NAFTCHI, N. (1959). *Amer. J. Cardiol.*, **4**, 580. 18 refs.

The authors of this paper from the Mount Sinai Hospital, New York, have carried out studies of the digital circulation in twenty patients with Raynaud's disease and 23 normal subjects. Measurements were made of the blood pressure and digital blood flow (by means of a calorimeter) at rest, after vasodilatation, and after the intravenous injection of L-noradrenaline.

The cases of Raynaud's disease could be divided into two groups, one with increased vasomotor tone but without digital vascular obstruction and the other with digital vascular obstruction and normal vasomotor tone. None of the patients in either group were significantly more sensitive to noradrenaline than the controls. The authors conclude that in Raynaud's disease the attacks are due either to obstructive digital arteriopathy or to digital vascular spasm due to increased sympathetic tone. It is suggested that the term Raynaud's disease or phenomenon be abandoned and the terms obstructive digital arteriopathy and neurogenic digital arterial spasm substituted. *I. McLean Baird.*

Method for the Functional Evaluation of Disability. SOKOLOW, J., SILSON, J. E., TAYLOR, E. J., ANDERSON, E. T., and RUSK, H. A. (1959). *Arch. phys. Med.*, **40**, 421. 10 refs.

Working at the Department of Physical Medicine and Rehabilitation, New York University, the authors have attempted to produce a method of recording objectively and in a uniform manner the physical, emotional, social, and vocational capacities of disabled persons. The form they have produced [which would appear to cover all the points and more] is therefore of vast proportions, each "master card" being coded for punching in eighty columns each containing twelve items; in addition a further "detail card" can be drawn up. In a trial of this form as a means of classifying the disability of 124 patients various examiners checked each others' assessments; agreement between such assessments was shown to be good. But the form illustrated in this paper is not the final one, the authors considering that several more points must still be added. A new form is therefore being devised and tested. *W. Tegner.*

Emotional Factor in Psoriasis. SUSSKIND, W., and MCGUIRE, R. J. (1959). *Scot. med. J.*, **4**, 503. 16 refs.

In a pilot investigation carried out at the Southern General Hospital, Glasgow, the authors attempted to determine the part played by psychological factors in psoriasis. Using the Maudsley Medical Questionnaire in a group of twenty patients with psoriasis, they found no significant incidence of psychoneurosis. On the other hand, stressful situations determined the onset or an exacerbation of the disease in a significant number of the patients. The possible relevance of dependency or of an immaturity factor was suggested by the fact that more than half the patients were the youngest in their sibship. Further detailed study of a larger series of patients is suggested. [There were no controls.] *John T. Ingram.*

Treatment of Psoriasis and Eczema with Grenz-rays. FRAIN-BELL, W., and BETTLEY, E. R. (1959). *Brit. J. Derm.*, **71**, 379. 4 refs.

At St. John's Hospital for Diseases of the Skin, London, a total of 192 patients, 87 with psoriasis and 105 with eczema, were treated with "soft" *x* rays (Bucky or Grenz rays) of which, it has been claimed, large total doses can be given without the risk of causing radiodermatitis.

Symmetrical bilateral eruptions were chosen for the trial whenever this was possible, equal doses being given to both sides, but with a lead screen inserted on one side, unknown to the patient. At first the dose of Grenz rays was 200 to 300 r. on three occasions at weekly intervals, but later the majority of the patients received 400 r. once a week for two or three exposures, since the lower dose had proved less effective. Treatment was with a standard Grenz-ray machine at 10 kV., HVL 0·02 mm. Al., and F.S.D. 30 cm.

Immediate improvement took place in 62 to 79 per cent. of the cases of psoriasis and in 67 per cent. of the cases of eczema, but this improvement was not maintained and at follow-up after 3 months these figures were reduced to 17 and 18 per cent. respectively. It appears therefore that Grenz-ray therapy has a useful though limited part to play in the management of psoriasis and eczema. *E. W. Prosser Thomas.*

Local Injection Therapy for Rheumatic Diseases. FINDER, J. G., and POST, M. (1960). *J. Amer. med. Ass.*, **172**, 2021. 18 refs.

Pleural Fluid Glucose with Special Reference to its Concentration in Rheumatoid Pleurisy with Effusion. CARR, D. T., and POWER, M. H. (1960). *Dis. Chest.*, **37**, 321. 14 refs.

Clinical Details and Discussion of the Therapeutic Action of the Combination of Vitamin B_{12}, Vitamin B_1, and Adenosine Monophosphoric Acid in Rheumatic Diseases. (Rilievi clinici e considerazioni sull'azione terapeutica dell'associazione vitamina B_1, vitamina B_{12}, acido adenosin-monofosforico nelle malattie reumatiche.) EINAUDI, G. (1960). *Gazz. med. ital.*, **110**, 57. 29 refs.

Cancer, Arthritis, and Rheumatoid Arthritis. (Cancer, Arthritis og Polyarthritis.) STRANDBERG, B., and JARLØV, N. V. (1960). *Ugeskr. Laeg.*, **122**, 568. 3 figs, 17 refs.

Psoriasis and Arthritis. REED, W. B., and BECKER, S. W. (1960). *A.M.A. Arch. Derm.*, **81**, 577. 4 figs, 26 refs.

Clinical and Therapeutic Contributions to the Relationship existing between Rheumatism and the Digestive Diseases. STOIA, I. (1960). *Rheumatism*, **16**, 51.

Neurogenic Arthropathy. KELLY, M. (1960). *Rheumatism*, **16**, 38. 3 figs, bibl.

Importance of Psychic Factors in the Pathogenesis and Treatment of Rheumatic Affections. (Importance des facteurs psychiques dans la pathogénie et le traitement des affections rhumatismales.) ORY, M., and RUELLE, M. (1960). *Rev. Rhum.*, **27**, 1. 31 refs.

Studies of Syndromes of Psychological Origin affecting the Locomotor System (Benign Dorsalgia and its Determining Factors). (Études sur les syndromes de l'appareil locomoteur d'origine psychique [Dorsalgie bénigne et ses facteurs déterminants].) ROTES-QUEROL, J., and CRESPI, P. B. (1960). *Rev. Rhum.*, **27**, 20. 21 refs.

Subungual Capillarogram in Rheumatoid Arthritis and in Disseminated Lupus Erythematosus. (El capilarograma subungueal en la artritis reumatoidea y en el lupus eritematoso diseminado.) LAPIDO, G., and FERRARI-FORCADE, A. (1959). *Arch. interamer. Rheum.*, **2**, 604. 3 figs, 29 refs.

Necrobiosis Lipoidica, Granuloma Annulare, and Rheumatoid Nodule. GRAY WOOD, M., and BEERMAN, H. (1960). *J. invest. Derm.*, **34**, 139. 3 figs, 23 refs.

Cutaneous Reaction to Streptochinase in Rheumatic Disease. (La reazione cutanea alla streptochinasi nella malattia reumatica.) LICHT, E., WYSOCKA, Z., and NOWOTARSKA, T. (1959). *Clin. pediat. (Bologna)*, **41**, 881. 4 refs.

Synovial Proliferation Induced by Polysaccharides. PAGE THOMAS, D. P., DINGLE, J. T., and COOK, E. R. (1960). *Nature (Lond.)*, **186**, 251. 1 fig., 6 refs.

"Acute Phase Reactants" in Rheumatic Diseases. DECKER, B., MCGUCKIN, W. F., MCKENZIE, B. F., and SLOCUMB, C. H. (1960). *Arthr. and Rheum.*, **3**, 49. 12 refs.

Ann. rheum. Dis. (1960), **19**, 297.

THE EXPERIMENTAL PRODUCTION OF ARTHRITIS

A REVIEW

BY

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The cause of rheumatoid arthritis remains unknown. For some years it has seemed that the pathogenesis of the disease might be more easily understood if a convenient animal replica were available for laboratory study. To this end much work on animal arthritis and the resultant considerable literature bear tribute. Nevertheless, it must reluctantly be admitted that not one of these forms of animal arthritis is strictly analogous to the human disease in which there is conclusive evidence neither of infection, of chronic physical or chemical irritation, of endocrine disturbance nor, in spite of suggestive serological changes, of causal immunological disorder.

The reasons determining this apparent inability to reproduce the disease in animals should be examined. That rheumatoid arthritis is a disease peculiar to the primates or to man is a possibility that has not been excluded. The value of further attempts to produce varieties of arthritis in small rodents must be seriously questioned. Consideration of this problem, and the need for promising lines of future inquiry have led the reviewer to gather together those methods which have previously been adopted for the laboratory study of arthritis. Previous surveys of the subject are listed in Table I.

No attempt has been made to divide the methods according to the purpose of the investigator, but for convenience the methods have been classified as infective, chemical, endocrine, immunological, and physical.

It is clear that the popularity of these experimental methods is determined by the particular era in which the work is performed, while the expressed purpose of the studies reflects contemporary interest in individual diseases. In the same way the animals chosen for investigation are usually those most easily available, cheapest, and most readily maintained, rather than those which would on theoretical grounds be expected to provide the most satisfactory analogy with the subjects of human disease. In many ways, therefore, the experimental study of arthritis has been handicapped by considerations irrelevant to the basic biological problems, and it is perhaps not surprising that the overall impression gained from a review such as this is of conflict, confusion, and stagnation. There is little doubt that future progress will depend upon more rational, more extensive and, almost certainly, less economical experimental design.

TABLE I

REVIEWS IN CHRONOLOGICAL ORDER

Author	Date	Subject
Redfern	1850	Experimental lesions of cartilage
Garrod	1859	Early nomenclature
Garrod	1876	Early nomenclature
Bannatyne	1896	Pathology of rheumatoid arthritis
Meyer	1901	Infective arthritis
Menzer	1902	Infective arthritis
Pommer	1929	Degenerative joint disease
Key	1930	Degenerative joint disease
Vannotti	1934	Allergic arthritis
Westcott	1941	General review
Findlay	1946	Pleuropneumonia-like organisms (P.P.L.O.)
Collins	1949	General review
Chevillard	1952	General review; measurement of responses
Dresner	1955	Aetiology of rheumatoid arthritis
Wilson and Miles	1955	Infective arthritis
American Rheumatism Reviews 1-12	1935-1959	*Ann. intern. med.*, 8-50. (13th review in preparation.)

I. EXPERIMENTAL PRODUCTION OF ARTHRITIS BY INFECTIVE AGENTS

The experimental study of infective arthritis began with the bacteriological era and historically has tended to follow the emphasis placed on organisms of diminishing size.

In the present account the infective agents used to induce arthritis are discussed in sequence according to their relative significance in contemporary research. The authors referred to in the following section are listed chronologically in Table II.

TABLE II

EXPERIMENTAL PRODUCTION OF ARTHRITIS BY INFECTIVE AGENTS

(1) *Pleuropneumonia-like Organisms*

Reviewed by Klieneberger (1940), Sabin (1941), Wallerstein and others (1946), Findlay (1946), and Dienes and Weinberger (1952).

Collier	(1938; 1939a to f)
Collier and Essefeld	(1938)
Findlay and others	(1939)
Collier and Staverman	(1939)
Rhodes and van Rooyen	(1939)
Sabin	(1938; 1939a, b; 1940)
Bonne	(1940)
Sabin and Warren	(1940)
Sabin and Johnson	(1940)
Preston	(1942)
Beeuwkes and Collier	(1942)
Powell and others	(1946)
Tripi and Kuzell	(1947)
Tripi and others	(1949)
Gardner and others	(1949)
Kuzell and Gardner	(1950)
Kuzell and Mankle	(1950)
Kuzell and others	(1951; 1952)
Parkes and Wrigley	(1951a)
Cordy and others	(1955; 1958)
Moulton and Adler	(1957)

Murphy Rat-lymphosarcoma Exudate Arthritis

Jasmin	(1956; 1957a, b)
Richer and Jasmin	(1957)
Hershberger	(1958)

(2) *Streptococci*

Early work reviewed by Meyer (1901) and by Menzer (1902), the more recent literature by Wilson and Miles (1955).

Bannatyne and others	(1896)
Shaw	(1904)
Cole	(1904)
Coombs and others	(1912)
Davis	(1912)
Jackson	(1913)
Schloss and Foster	(1913)
Rothschild and Thalhimer	(1914)
Thalhimer and Rothschild	(1914)
Nathan	(1917)
Cecil	(1931)
Hadjopoulos and Burbank	(1932)
Rinehart and others	(1934)
Rinehart	(1935)
Rawls and Chapman	(1935)
Schultz	(1936)
Brinch	(1936)
Cecil and others	(1939)
Rothbard	(1940)
Angevine and others	(1942)
Friedlander	(1951)
Friedlander and others	(1951b)
Benko and others	(1953)
Smirnov and Beletskaia	(1955)

(3) *Erysipelothrix rhusiopathiae*

Goret and Jean	(1934)
Collins and Goldie	(1940)
Goldie and Collins	(1951; 1956)
Hughes	(1955)
Sikes and others	(1955a, b; 1956; 1957)

(4) *Other Pyogenic Organisms*

Lion	(1890)
Buday	(1890)
Saint-Germain	(1893)
Lanz	(1893)
Bannatyne and others	(1896)
Michaelis	(1897)
Triboulet	(1898)
Apert	(1898)
Poynton	(1898; 1899)
Westphal and others	(1899)
Poynton and Payne	(1900a, b, c, d, *et seq.*)
Beaton and Walker	(1903)
Beattie	(1904)
Nathan	(1917)
Brunschwig and Jung	(1931)
Svartz	(1938)
Cecil and others	(1939)
Rigdon	(1942)
Friedlander	(1951)
Friedlander and others	(1951b)

(5) *Streptobacillus moniliformis*

Levaditi and Selbie	(1930)
Levaditi and others	(1930)
Buddingh	(1944)
Levey and Levey	(1948)
Freundt	(1956a, b)

(6) *Tubercle bacillus*

Schüller	(1880)
Krause	(1899)
Griffith	(1925)
Blacklock	(1957)

(7) *Mycotic Arthritis*

Pepere	(1913)
Bolognesi	(1923)
Gammel and Moritz	(1933)
Lorizio	(1939)
Jasmin	(1957b)

(8) *Typhoid bacillus*

Molinari and Dusso	(1933)

(9) *Corynebacteria*

Levaditi and others	(1931)
Fischl and others	(1931)
Friedlander and others	(1951a)

(10) *Viruses*

Sokoloff and Beegel	(1953)

(1) Pleuropneumonia-like Organisms (Nocard and Roux, 1898).—An extensive literature deals with the relationship of the pleuropneumonia-like organisms (P.P.L.O.) to spontaneous and experimental arthritis. Comprehensive accounts of the nature of the P.P.L.O., of their distribution, and of their relationship to arthritis in man and animals have been given by Klieneberger (1940), Sabin (1941), Wallerstein, Vallee, and Turner (1946), Findlay (1946), and Dienes and Weinberger (1952).

Interest in the association of the P.P.L.O. with arthritis began in 1938-1939. Findlay, Mackenzie, MacCallum, and Klieneberger (1939) referred to the papers of Collier (1938, 1939a) describing an outbreak of spontaneous rat polyarthritis in the Dutch East Indies. Organisms grown in the laboratory and resembling the L.5 group of Klieneberger reproduced the disease after inoculation. Collier's observations were dealt with most fully in a series of reports (Collier, 1938; Collier and Esseveld, 1938; Collier, 1939a-f; Collier and Staverman, 1939); they were outlined in English (Collier, 1939a) and the whole problem was revived in the post-war period (Collier, 1948) in relation to a mouse epizootic. The histological changes found in the rat joints were detailed by Bonne (1940), who regarded them as an osteosynovitis rather than

as an arthritis and described the resulting exuberant osteophytosis.

A similar outbreak of arthritis in the rat was reported by Rhodes and van Rooyen (1939). Arthritis progressed to healing or to spontaneous amputation. The disease was thought to be similar to that caused by *Streptobacillus moniliformis*, and to that caused by *Ectromelia* in mice, but neither of these organisms was identified. The disease could be transmitted to rats, but not to mice. Sabin (1939a, b) described a form of progressive, proliferative arthritis produced in mice by a P.P.L.O. and likened the disease to rheumatoid arthritis. In another paper (Sabin, 1938), he reported a strain which multiplied in brain as well as on serous surfaces. The treatment of mouse P.P.L.O. arthritis was first investigated by Sabin and Warren (1940) using aurothioglycolate compounds. Paradoxically, these chemicals did not inhibit the growth of P.P.L.O. *in vitro*, but might produce cure of the arthritis. Sabin and Johnson (1940) searched for the organism in cases of Reiter's disease and in rheumatoid arthritis, after Sabin (1940) had described a progressive arthritis in the experimentally infected mouse. Their work emphasized the similarity of the disease to rheumatoid arthritis. Preston (1942), however, found that the inflammatory lesions were principally periarticular and that with increasing virulence the incidence of arthritis diminished. Beeuwkes and Collier (1942) cautiously compared two strains of P.P.L.O. isolated from spontaneous rat polyarthritis and from rats inoculated with material from a case of rheumatic arthritis, but the concensus of opinion (Tripi, Gardner, and Kuzell, 1949) preferred to accept animal P.P.L.O. infections as useful experimental models rather than as exact replicas of any particular human disease. Thereafter the majority of workers used experimental P.P.L.O. arthritis in this way to evaluate therapeutic agents. However, Cordy, Adler, and Berg (1958) (see also Cordy, Adler, and Yamamoto, 1955) passaged goat P.P.L.O. through lambs and found that injection into pigs caused arthritis, serositis, and meningitis, while Moulton and Adler (1957) demonstrated the production of arthritis in chick-embryos inoculated with P.P.L.O. Streptomycin and myocrisin were shown to be effective means of treating experimental P.P.L.O. arthritis (Powell, Jamieson, and Rice, 1946) following the earlier work of Findlay and others (1939), and of Sabin (1940), on the value of gold and of sulphonamides, and that of Snow and Hines (1941) on the influence of obstructive jaundice (Engerman and Meyer, 1959). Tripi and Kuzell (1947) confirmed the value of gold, but Gardner, Fairley, and Kuzell (1949) adopted the reciprocal approach and showed that animals treated with B.A.L. (dimercaprol) had a higher incidence of severe arthritis than controls. Exposure to cold (70° F.) and to ultraviolet light curiously reduced the incidence and severity of arthritis. Similar observations were made with salazopyrin (Kuzell and Gardner, 1950), terramycin, aureomycin, cortisone, and ACTH (Kuzell and Mankle, 1950; Kuzell, Schaffarzick, Mankle, and Gardner, 1951), and organic copper salts. This work was later reviewed (Kuzell, Gardner, Fairley, and Tripi, 1952). It formed the background for studies of a similar nature (Parkes and Wrigley, 1951a) in which the candid conclusion was reached that the histological changes were not sufficiently similar to those of rheumatoid arthritis to provide a valid model.

Jasmin (1956) described a polyarthritis in the rat resulting from injecting the exudate from a pouch bearing the Murphy rat lymphosarcoma. Whether the resulting arthritis was anaphylactic (Jasmin, 1957a, b) or infective (Richer and Jasmin, 1957) was not clear, but there was a good response to cortisol (Hershberger, 1958).

(2) Streptococci.—The early work on the experimental production of infective arthritis, confused by differences of nomenclature, was reviewed by Meyer (1901), and by Menzer (1902). Bannatyne, Wohlmann, and Blaxall (1896) used organisms isolated from a patient with "rheumatism"; streptococci were employed in a similar manner by Shaw (1904) and Harris (1905). Cole (1904) described related experiments but disagreed with the concept of a *Diplococcus rheumaticus* specific to acute rheumatism. Coombs, Miller, and Kettle (1912) and Davis (1912) reported the production in rabbits of lesions resembling those of rheumatic fever. Jackson (1913) injected rabbits with streptococci recovered from a human outbreak; she found evidence of arthritis when the animals were examined at intervals up to 4 months after the injections. Single or repeated intravenous injection of streptococci led Schloss and Foster (1913) to the production of both acute and chronic polyarthritis in monkeys. The chronic articular lesions were nonspecific. Rothschild and Thalhimer (1914) and Thalhimer and Rothschild (1914) confirmed the observations of Cole (1904) and of Davis (1912) and claimed that half the rabbits they injected with *Streptococcus imitis* developed an arthritis similar to that found in human infections with the same organism. They agreed that it was unjustifiable to postulate a special variety of organism on the basis of a capacity to pro-

duce arthritis. Nathan (1917) made experiments of a generally similar nature, but used other pyogenic organisms in addition to streptococci. Hadjopoulos and Burbank (1932) gave convincing evidence that a subacute arthritis could be produced in rabbits by inoculating streptococci of low virulence isolated from cases of chronic febrile arthritis. They concluded that the changes were the direct result of local infection and not of allergy. Rinehart, Connor, and Mettier (1934) considered the relationship between infection and scurvy.

Previous attempts to reproduce acute rheumatism had been unsuccessful, but the influence of subclinical ascorbic acid deficiency was believed to predispose to the development of lesions resembling those of rheumatoid arthritis (Rinehart, 1935). Their suggestion that the arthritis of rheumatoid arthritis is simply the result of subclinical scurvy modified by streptococcal infection has not been substantiated. Pirani, Bly, and Sutherland (1950) extended the study of scorbutic arthropathy to the guinea-pig. Rawls and Chapman (1935), quoting the work of Cecil, Nicholls, and Stainsby (1931), divided a series of streptococci into those which were agglutinable and those which were inagglutinable and resistant to the bactericidal action of fresh blood. Intravenous injections into rabbits showed that more than 90 per cent. of the inagglutinable strains produced arthritis. It seems likely that the reactions observed were simply a measure of virulence. Schultz (1936) made similar studies with Group C streptococci. Using scorbutic guinea-pigs, he found only slight arthritic changes and could not relate them to the presence of infection. A simple account of the histological changes in experimental streptococcal arthritis was given by Brinch (1936), who emphasized the resemblance to degenerative joint disease rather than to rheumatoid arthritis. Dawson (1937) reviewed the evidence implicating streptococci in the pathogenesis of rheumatoid arthritis; he emphasized that no final conclusion could be reached. The work of Cecil, Angevine, and Rothbard (1939), in which haemolytic streptococci were used to cause arthritis in rabbits, led these authors to conclude that the lesions found, although resembling those of rheumatoid arthritis, were not specific. Their work was continued by Rothbard (1940) using the albino rat, and by Angevine, Cecil, and Rothbard (1942) using the rabbit. Rothbard (1940) found that most rats injected with virulent human streptococci developed a purulent arthritis. Blakemore, Elliott, and Hart-Mercer (1941) reported the changes found in joint-ill in lambs, a suppurative arthritis which develops during the first month of life following the infection of wounds with a variety of organisms, of which streptococci are the most frequent. This work has not, so far as I am aware, been made the basis of an experimental study. Friedlander (1951) and Friedlander, Habermann, and Parr (1951b) included haemolytic streptococci among the pyogenic organisms they studied, and a discussion of the effect of Weld's streptotoxin on experimental arthritis was given by Benko, Boszormenyi, Olah, Csati, and Szeitz (1953). Smirnov and Beletskaia (1955) found that deoxycortone (cortexone) exacerbated the arthritis caused in rats by β-haemolytic streptococci.

(3) ***Erysipelothrix rhusiopathiae.***—The paper by Goret and Jean (1934) on the *Bacillus du rouget* or *Erysipelothrix rhusiopathiae* in naturally-occurring swine arthritis at first attracted little attention among those investigating the pathology of rheumatic disease. Joint disease in the rabbit followed intra-articular, subcutaneous, intradermal, or intravenous inoculation. Optimal results were obtained by injecting sublethal inocula subcutaneously. Collins and Goldie (1940) made a detailed study of the infection in swine and of the polyarthritis. They were able to reproduce the disease by the repeated intravenous injection of *Erysipelothrix rhusiopathiae* into each of eight animals. Hypersensitivity was not a prerequisite for the appearance of the chronic proliferative arthritis. Bacteriaemia followed injection; the organism could be isolated from the joints for up to 8 months afterwards. Goldie and Collins (1951) reported similar studies with rabbits. Intravenous inocula much smaller than those which effectively produced pathological changes resulted in arthritis in fourteen of fifteen rabbits. As is commonly the case in the experimental study of arthritis, the clinical recognition of the arthritis was difficult: the need for histological confirmation was emphasized. Ten of the 26 knee joints so studied were found to be diseased. Subsequently (Hughes, 1955; Sikes, Neher, and Doyle, 1956) interest in this disorder increased. Sikes, Neher, and Doyle (1955a) recovered the organism from hogs with the naturally-occurring infection; intra-articular injection was an effective means of infecting unexposed shoats.* Cortisone but not ACTH caused remission (Sikes, Neher, and Doyle, 1955b), while cortexone augmented the disease (Sikes, Neher, and Doyle, 1957). Contrary to this work, Goldie and Collins (1956) showed that in rabbits cortisone favoured the development of arthritis following small repeated inocula.

* shoats: young hogs.

The experimental inoculation of *Erysipelothrix rhusiopathiae* into young hogs or into rabbits offers a method of reproducing a disease in which the joints show many of the histological changes found in rheumatoid arthritis in the human. However, many of these characteristics of rheumatoid arthritis are, in themselves, non-specific; since no organisms have been identified in the human disease, the pursuit of this experimental replica can be regarded only as principally of theoretical interest.

(4) Other Pyogenic Organisms.—The earlier literature contains many undocumented references to studies of suppurative arthritis (Lion, 1890; Buday, 1890; Saint-Germain, 1893; Lanz, 1893; Michaelis, 1897; Triboulet, 1898; Apert, 1898; Westphal, Wassermann, and Malkoff, 1899). Bannatyne, Wohlmann, and Blaxall (1896) were among the first to describe the experimental production of a suppurative arthritis by the intravenous inoculation of rabbits with organisms, probably bacilli, recovered from the synovial fluid of a patient with "rheumatism" (probably rheumatic fever). A similar approach was adopted by Poynton (1898, 1899), Poynton and Payne (1900a, b, c, d, *et seq.*), Beaton and Walker (1903), and Beattie (1904). The work of Poynton and Payne (1900) gained considerable notoriety. They concluded, on the basis of experiments conducted with rabbits, that human rheumatic fever was the result of infection with a "*Diplococcus rheumaticus*", an organism isolated from human cases of this disease which would cause a purulent arthritis in rabbits. A similar form of suppurative bacillary polyarthritis had been produced by Lanz (1893). Nathan (1917) repeated this work, using a variety of organisms including streptococci, staphylococci, and pneumococci. The work of Brunschwig and Jung (1931) suggested for the first time that certain of these pyogenic infections might not be due directly to bacterial invasiveness. Microscopical lesions in rabbit joints identical with those seen after intravenous or intra-articular administration followed the injection of a 7-day culture after filtration through a Chamberland L3 filter. The authors suggested the action of a staphylococcal toxin. In discursive and poorly illustrated papers, Svartz (1938) reported the production of polyarthritis by the repetitive inoculation of an emulsion of the polymorphic diplococci isolated from patients with polyarthritis; she concluded that the changes resembled those of human rheumatism. Cecil, Angevine, and Rothbard (1939) found lesions in rabbits after the repeated intravenous injection of *Streptococcus viridans*, staphylococci, pneumococci, and *Salmonella paratyphi A*, histologically similar to the non-specific changes they associated with rheumatoid arthritis. Rigdon (1942) contrasted the response of actively and passively immunized rabbits to the intravenous inoculation of a broth culture of *Staphylococcus aureus*, and Friedlander (1951) and Friedlander, Habermann, and Parr (1951b) used the albino rat and mouse in a survey of the effects of haemolytic streptococci. A statistically significant increase in the incidence of arthritis was produced by previous treatment with cortisone acetate.

Neither staphylococci, nor any of the organisms studied in these papers, can be held responsible for rheumatoid arthritis, although they may be secondary invaders. Work on experimental pyogenic arthritis can be accepted as relevant only to the now unimportant problem of human suppurative arthritis (Kellgren, Ball, Fairbrother, and Barnes, 1958).

(5) *Streptobacillus moniliformis*.—Among the lesions described by Levaditi and Selbie (1930), and by Levaditi, Selbie, and Schoen (1930), in mice spontaneously or experimentally infected with *Streptobacillus moniliformis*, were polyarthritis of the vertebral column and subcutaneous nodules. The microscopical appearances were considered to be similar to those of acute or of chronic human arthritis but knowledge of the possible role of P.P.L.O. in mouse arthritis came only later. Survival, which was rare, was accompanied by a deforming arthritis. Buddingh (1944) made an important contribution in his study of the infected chick-embryo, using a strain derived from a human case of rat-bite fever. In the chick, blood stream invasion was followed by almost exclusive localization of the organisms in the synovial membranes of joints, in the lining cells of which the organism behaved as a facultative intracellular parasite. Infected mice were effectively treated with streptomycin (Levey and Levey, 1948). Freundt (1956a, b) described a mouse epizootic due to the same organism. The disease was quickly fatal; arthritis was uncommon. Spontaneous amputation of infected limbs characterized the natural but not the experimental infection.

Because of its tendency to localize in joints with synovial cavities, and because of the resemblance of some of the resulting histological changes to those of rheumatoid arthritis, *Streptobacillus moniliformis* may be thought to provide as satisfactory a replica of the human disease as any other known organism. It is clear again, however, that information derived

from such infections can be applied to the problem of rheumatoid arthritis only with the greatest caution.

(6) Tubercle Bacillus.—Following the work of Schüller (1880), Krause (1899) showed that infection in rabbit and guinea-pig bones rarely occurred at the sites of fractures but was common in joints which had been distorted. The whole problem of trauma in relation to experimental infective tuberculous arthritis was reviewed by Blacklock (1957). Griffith (1925) made the interesting discovery that avian tubercle bacilli injected into rabbits were localized within the joints in each instance. The relevance of this work to the common problems of human polyarthritis is uncertain.

(7) Mycotic Arthritis.—The fungus of mycetoma, *Monosporium apospermium*, was used by Pepere (1913) to produce a purulent arthritis in rabbits, and Bolognesi (1923) made a study of seven fungi and caused a mycotic arthritis in albino rats which occasionally resolved spontaneously. Gammel and Moritz (1933) demonstrated the destruction of articular cartilage in rabbits following the intra-articular injection of *Actinomyces asteroides* and of *Monosporium apospermium*. Granuloma formation was accompanied by bone absorption and necrosis.

In the course of a series of experiments on the properties of *Nocardia sanfelice*, Lorizio (1939) injected the knee joints of rabbits with a culture of the streptothrix. Although the lesions found were those of a subacute inflammation, becoming chronic, a possible similarity to chronic forms of human arthritis was not remarked. More recently *Nocardia asteroides* has been invoked as an explanation for the arthritis caused by the Murphy rat-lymphosarcoma exudate (Jasmin, 1957b).

The incidence of human mycotic arthritis has risen in recent years, but in the reviewer's experience the infection is more likely to be an associated complication of rheumatoid arthritis than to bear any causal relationship.

(8) Typhoid Bacillus.—In an original approach, Molinari and Dusso (1933) attempted to produce an arthropathic strain of typhoid bacilli by growing virulent bacilli in a medium containing articular extracts. 1 ml. broth culture was injected into the knee joints of rabbits. The claim was made that such organisms, after passage, were organotropic. However, the arthritis was suppurative and mono-articular. This work apparently has not been repeated, but recalls the later experiments of Glynn and Holborow (1952) and of Boake and Muir (1955).

(9) *Corynebacteria*.—Although the claim of Levaditi (1931) that the causative agent of mouse arthritis was a coccobacillus and that of Fischl, Koech, and Kussat (1931) that the infection was due to *Corynebacteria* were both suspect because of the subsequent discovery in arthritic mice of P.P.L.O., further studies of a *Corynebacteria*-like organism isolated by Friedlander, Habermann, and Parr (1951a) showed that this organism could be used to induce a previously undescribed form of polyarthritis in white rats.

(10) Viruses.—Sokoloff and Beegel (1953), in a survey of viruses of rabbit vaccinia, infectious myxomatosis, and virus III, demonstrated that the local injection of these organisms caused an arthritis in rabbits. Trauma to the joints before systemic viral infection, and the local injection of the growth products of Group A streptococci did not cause the virus infection to localize.

Comment

Many forms of infective arthritis have been studied experimentally, principally in mice, rats, and rabbits. These infections provide easily reproducible models of arthritis for laboratory study, and for the testing of analgesic, anti-inflammatory, and chemotherapeutic agents. It remains to be demonstrated that any of these infections is in any way relevant to the problem of rheumatoid arthritis in the human.

II. Experimental Production of Arthritis by Chemical Agents (Table III)

Arthritis produced by the direct application of chemical irritants alone or in combination with physical stimuli has been studied experimentally for at least 100 years. The method is simple and reproducible, but the changes caused have never gained easy acceptance as true replicas of the common forms of chronic human arthritis. This limitation has not deterred first, the student of degenerative joint disease, and secondly, and more recently, the student of rheumatoid arthritis. The diversity of agents employed covers an extraordinary range. In this review the classification of agents as physical or chemical has been adopted for convenience, although, owing to the preconceptions of investigators, it often reflects specific

attempts to reproduce degenerative joint disease or rheumatoid arthritis respectively.

TABLE III

PRODUCTION OF EXPERIMENTAL ARTHRITIS BY CHEMICAL AGENTS

(1) *Distilled water; sodium chloride solution*
- Key (1933)

(2) *Acids; Alkalis*
- Riedel (1896)
- Burckhardt (1924)
- Seeliger (1926)
- Häbler (1928)
- Key (1933)

(3) *Other Protein-Denaturing Agents*

(*a*) *Xylene, turpentine*
- Jordan (1938)
- Ramsey and Key (1955)

(*b*) *Formaldehyde*
- Selye (1949)
- Brownlee (1950)
- Frenk and others (1950)
- Fachini and others (1950)
- Uebel and Korting (1950)
- Amante and Bidone (1950)
- Dugal (1951)
- Parkes and Wrigley (1951b)
- Anttonen and others (1951)
- Bourne (1951)
- Gallini and Grego (1951)
- Madonia (1952)
- Gubner and others (1952)
- Bacchus (1952)
- Gaglio and others (1953)
- Zorn and others (1953)
- Blech and Emrich (1954)
- Bonomo and Chirico (1954)
- Gaglio and Leonardi (1954)
- Saric and others (1954)
- Radino and Bagolan (1954)
- Zorn and Mankel (1954)
- Conti (1954)
- Gerocarni and Calderera (1956)
- Farneti and Miccoli (1956)
- Vykydal and others (1956)
- Gujral and Saxena (1956)
- Maschio and Boschi (1956)
- Zorn and Schmidt (1957)
- Zorn (1958)
- Gujral and others (1959)

(*c*) *Iodine*
- Riedel (1896)
- Burckhardt (1924)
- Key (1930)

(4) *Other Organic Chemicals*

(*a*) Indole, skatole; Indole propionic acid; Tryptamine — Forbes and Neale (1937)

(*b*) Streptococcal toxin; Diphtheria, tetanus, staphylococcal toxoids; Tyramine and other substances; Cortisone, testosterone; Trypsin, gastric mucin; Bacterial mucopolysaccharides; Hyaluronic acid; Friedlander's bacillus, streptococcal vaccines — Jones and Carter (1954)

(*c*) *Histamine*
- Uebel and Korting (1950)
- Jones and Carter (1954)
- Bensley (1955)

(*d*) *Scorbutic Arthropathy*
- Rinehart (1935)
- Schultz (1936)
- Pirani and others (1950)

(*e*) *Proprionitriles*
- Wawzonek and others (1955)

and many subsequent papers

(*f*) *Papain*
- Thomas (1956)

(*g*) *Caragheenin*
- Williams (1957)
- Gardner (1957a; 1960)

(*h*) *Hydralazine*
- Comens (1956)
- Gardner (1957b)
- Dubois and others (1957)

(*i*) *Mustard*
- Coutu and Selye (1950)
- Teodoru and others (1952)
- Ducommun and Coutu (1952)
- Ducommun and others (1952)
- Coutu and others (1953)
- Radino (1957)

(1) Injection of Distilled Water or of Sodium Chloride Solution.—As part of an extensive series of investigations into the factors determining degenerative joint disease, Key (1933) injected distilled water, and normal or 10 per cent. sodium chloride into the knee joints of rabbits. Distilled water produced thickening of synovial tissues and an excessive amount of fluid, but, strangely, the changes found with normal sodium chloride were more severe. The conclusion that such lesions resembled those of osteo-arthritis should probably be interpreted as an indication only of their non-specificity.

(2) Injection of Acids or of Alkalis.—Burckhardt (1924) attempted to define the conditions necessary for the production of arthritis deformans in various species. He injected carbolic acid into the limb joints of guinea-pigs, rats, rabbits, and dogs. The work was essentially a repetition of that of Axhausen (1913), who supported the theory that for degenerative joint disease to develop a nidus of dead articular cartilage was necessary. Burckhardt explored the role of immobilization of the joint on the evolution of arthritis by suturing limbs beneath the skin, by cutting the motor nerves (see Nozoe, 1938), and by placing a metal ring round the flexed limb. Seeliger (1926) attributed degenerative joint disease to acidity of the synovial fluid and attempted to reproduce the disease in rabbit knee joints by injecting N/50 hydrochloric acid. Villous hyperplasia and replacement fibrosis of articular cartilage led him to judge his theory to be supported by these results. The work was repeated by Häbler (1928), who noted that distilled water caused more rapid and more severe damage than acid, suggesting the importance of a disturbed colloid state and altered cartilaginous elasticity rather than of a simple change in acidity. Key (1933) used caustic soda, and lactic, acetic, or hydrochloric acids for a similar purpose, experiments deriving from the bizarre combination of caustics and heat said by Mannheim (1929) to have been studied by Kremjanski (1868).

Riedel (1896) reported work with caustic ammonia or tincture of iodine. The appearances of the

degenerating articular cartilage resembled the non-specific lesions produced by electrolysis (Axhausen, 1913, 1914).

Fischer and Timbrell (1927) are reported by Mannheim (1929) as authors of work on experimental arthritis with radium bromide. As far as the reviewer is aware this is the only instance in which local irradiation has been used for this purpose.

(3) Other Protein-Denaturing Agents.—Although Jordan (1938) had used xylene and turpentine (*a*) in his studies, it was the adoption by Selye (1949) of formaldehyde (*b*), as a means of inducing what he termed a self-perpetuating arthritis in the rat, which popularized protein-denaturing agents as tools for causing experimental chemical arthritis.

Selye showed, not surprisingly, that formaldehyde injected around the limb joints of rats caused acute inflammation. Large doses induced a more chronic lesion with oedema, hyperaemia, connective tissue proliferation, and stiffness. Relating this work to his earlier studies on hormone-induced arthritis (Selye, Sylvester, Hall, and Leblond, 1944), Selye claimed that the formaldehyde arthritis was aggravated by deoxycortone acetate (cortexone) or by crude anterior pituitary preparations, but was almost completely inhibited by cortisone or by ACTH, suggesting an antagonism between the two groups of hormones.

A spate of papers followed. A few workers showed that some of the essential conclusions on which Selye based his theories could not be substantiated. Many others greeted Selye's work with less discretion and elaborated his hypotheses. Brownlee (1950) confirmed that formalin injected beneath the plantar aponeurosis of the rat caused arthritis. In adrenalectomized animals he compared the influence of deoxycortone and of ascorbic acid, concluding that deoxycortone exacerbates the arthritis in normal rats but less severely in adrenalectomized animals. Frenk, Wolfe, and Paschkis (1950) could not relieve the arthritis with deoxycortone and ascorbic acid. Fachini, Ceresa, Rubino, and Morpurgo (1950), Amante and Bidone (1950), Uebel and Korting (1950), Gallini and Grego (1951), Anttonen, Rinne, and Rinne (1951), Gaglio, Mazzone, and Leonardi (1953), Bonomo and Chirico (1954) extended Selye's work. By contrast, Parkes and Wrigley (1951b) failed to show that ACTH or cortisone alleviated the arthritis, but confirmed that deoxycortone exaggerated local swelling. Bourne (1951) was unable to define the self-perpetuating chronic arthritis likened by Selye to rheumatoid arthritis, and confirmed in fact that the arthritis was usually more accurately described as a periarthritis. Frequently the joints were not directly involved and neither cartilaginous erosion nor granulation tissue could be found. Dugal (1951), however, showed the aggravating effect of cold on the formalin-induced swelling, and the ameliorating effect, in adult rats, of ascorbic acid. Madonia (1952) suggested that methyl thiouracil acted *via* the pituitary/adrenal axis in suppressing the development of formalin arthritis. Gubner, Cote, Hughes, Oleson, Ruegsegger, and Williams (1952) confirmed the benefits of cortisone and of ACTH. Bacchus (1952) found that ascorbic acid did not influence the formalin changes in adrenalectomized rats, suggesting that ascorbic acid acted on the intact adult animal by influencing the adrenal cortical hormones. Formalin arthritis was studied by Zorn, Plagwitz, Wolf, Kraul, and Schirmeyer (1953) and by Saric, Tessier, Rivière, and Bertharion (1954), principally from the aspect of treatment with drugs like isonicotinic acid hydrazide. Not unexpectedly, Radino and Bagolan (1954) showed that ultrasonic vibration caused exacerbations of both formalin and serum arthritis. Zorn and Mankel (1954), Zorn and Schmidt (1957), and Zorn (1958) continued their therapeutic studies with quinoline derivatives, with female sex hormones, and with harpagophytum root, but made no real contribution to our knowledge of the pathogenesis or therapy of the human disease. Adenosine triphosphoric acid was used by Conti (1954), and phenylbutazone by Gaglio and Leonardi (1954) in similar observations, while Blech and Emmrich (1954) showed that partial hepatectomy 1 or 2 days before the injection of formalin reduced the resistance of animals to the inflammatory agent. More recently, a variety of additional therapeutic agents, including cortisone and vitamin B_6 (Gerocarni and Calderera, 1956), heavy metals (Vykydal, Klabusay, and Trnavsky, 1956; Farneti and Miccoli, 1956), cortisone, phenylbutazone, myocrisin, and salicylates (Gujral and Saxena, 1956), and extracts of *Glycyrrhiza glabra Linn.* (Gujral, Sareen, Tangri, Roy, Gupta, and Amma, 1959), have been used in similar experiments. Maschio and Boschi (1956) compared a formalin arthritis of rabbits with the arthritis caused in dogs by the local resection of cartilage (see Kroh, 1909).

Like the majority of chemical agents employed to cause experimental arthritis, formalin has been used in experiments made in most instances to fit preconceived theories, and not simply to test unsubstantiated hypotheses; this has led to a considerable volume of work on the pathogenesis of arthritis in the rat but little of this can be accepted as immediately relevant to the problem of rheumatoid arthritis in man. The use of formalin invites

comparison with earlier work designed to produce osteo-arthritis (Axhausen, 1913; Pommer, 1915), and its local influence is open to critical assessment because of the demonstration that its action is often to produce periarticular rather than articular inflammation, doubtless because of the difficulty of making true intra-articular injections into small rodents.

(4) Other Organic Chemicals

(*a*) The demonstration of excessive amounts of indole in the urine of patients with rheumatoid arthritis led Forbes and Neale (1937) to inject indole, skatole, and indole propionic acid into the joints of rabbits, producing a chronic arthritis. No far-reaching conclusions were drawn; neither the design nor the prosecution of this experiment stand close scrutiny.

(*b*) Very many other organic chemicals and extracts, the majority ineffective (Table III, 4*b*), were used by Jones and Carter (1954) in an attempt to find a reproducible form of arthritis in the guinea-pig. Mucopolysaccharides from various sources were effective in causing occasional synovial lesions, but the changes were not specific, were not associated with anaphylaxis, and often developed before antibody formation was demonstrable. Work with the polysaccharide extracts of Friedlander's bacillus (Jones, Carter, and Rankin, 1954) led to a series of important observations (Jones and Carter, 1957a, b; Jones and Mayne, 1958), in which the evolution of the arthritic lesions in the guinea-pig was studied with ^{14}C-labelled polysaccharide, and in which the modifying influences of cortisone and of ACTH on the mucopolysaccharides of the involved tissues were investigated.

(*c*) Bensley (1955) discussed the factors involved in the production of arthritis by histamine, a drug which had also been studied by Uebel and Korting (1950) and by Jones and Carter (1954). Local inflammatory and generalized endocrine changes were caused by single or repeated injections of sterile isotonic histamine acid phosphate; the chronic changes resembled those of human arthritis.

(*d*) It is probably desirable to refer at this point to the view of Rinehart (1935) that the lesions of rheumatoid arthritis were mimicked by those of experimental scurvy (Schultz, 1936; Pirani, Bly, and Sutherland, 1950); this opinion did not take sufficient account of the non-specificity of many of the lesions in the human disease, and the published illustrations were not sufficiently clear to confirm or refute this theory.

(*e*) The recent interest in experimental lathyrism (Wawzonek, Ponseti, Shepard, and Wiedenmann, 1955) drew attention to a means of causing experimental maldevelopment of joints and ligaments. The effective proprionitriles have not apparently been used in conjunction with agents specifically damaging joint tissues such as anti-synovial antisera.

(*f*) It is not clear whether the necrosis of rabbits' ear cartilage caused by papain (Thomas, 1956) offers an approach to this problem.

(*g*) The reviewer has found it convenient to employ the highly sulphated mucopolysaccharide carragheenin (Jackson, 1956a, b; Williams, 1957) as an agent to produce arthritis in rabbits and guinea-pigs (Gardner, 1957a, 1960). Repetitive periarticular injections lead to sustained synovial inflammation; in selected microscopic fields it is found possible to locate changes indistinguishable from those commonly seen in rheumatoid arthritis in the human (Gardner, 1960). Such changes, however, are individually not specific.

(*h*) Considerable interest was aroused by the description of the hydralazine syndrome (Dustan, Taylor, Corcoran, and Page, 1954), but the enthusiastic description of an experimental form of systemic lupus erythematosus (Comens, 1956) has not been confirmed (Gardner, 1957b; Dubois, Katz, Freeman, and Garbak, 1957), and joint changes analogous with those of the human disease (Cruickshank, 1959) have not been found.

(*i*) The use of mustard in causing an experimental arthritis was popularized by Coutu and Selye (1950), who injected 0·1 ml. of a 10 per cent. mustard suspension into eighteen intact rats and eighteen adrenalectomized rats. The authors were unable to confirm the claim of Brownlee (1950) that deoxycortone and ascorbic acid were beneficial. Teodoru, Feyal-Cabanes, and Jequier (1952), studying mustard arthritis, showed that chloramphenicol did not influence the anti-inflammatory effect of cortisone in spite of its stimulating effect on the reticulo-endothelial system. Ducommun and Coutu (1952) observed the effect of fasting on mustard arthritis, and Ducommun, Jacot, Coutu, Koch, and Selye (1952) compared the anti-inflammatory effects of irgapyrine and phenergan on the same condition; these anti-inflammatory effects could be produced in adrenalectomized rats. Coutu, Gareau, and Ducommun (1953) claimed that deoxycortone exaggerated the arthritic response which was minimized by cortisone. It is clear from the illustrations in this and in earlier papers that the mustard arthritis induced in rats was a poor replica of

rheumatoid arthritis in man. Coutu, however, emphasized that the differences were quantitative and not qualitative, a point which requires objective confirmation or refutation. Later, Radino (1957) extended her study of the effects of ultrasonics to mustard arthritis, including work on the histochemistry of the connective tissues.

Comment

Several organic and inorganic chemicals may be used to induce convenient forms of experimental arthritis in small laboratory animals. These forms of arthritis provide acceptable models for the study of the pathological physiology of joint disease, but none can be regarded as reduplicating in detail the evolution and behaviour of rheumatoid arthritis.

III. Experimental Production of Arthritis by Altered Endocrine Mechanisms (Table IV)

(1) Action of Deoxycortone Acetate in Normal Rats.—The possibility that arthritic changes resembling those of rheumatic fever and of rheumatoid arthritis might be produced experimentally by altered endocrine function was suggested by Selye (Selye and Hall, 1943; Selye and Pentz, 1943; Selye, Sylvester, Hall, and Leblond, 1944). The production of joint lesions in rats by giving very large amounts of deoxycortone acetate (cortexone) was described. In the original report three animals out of eight given deoxycortone developed arthritic changes; these changes appeared within 10 days of starting treatment, and subsided and reappeared in different joints without obvious reason. Many animals in the colony died from intercurrent infection and the possible role of infection in causing arthritis was not given sufficient consideration. From this work, which included studies of adrenalectomized and of thyroidectomized animals, the conclusion was drawn that the adrenal cortex plays an important part in the pathogenesis of rheumatic fever and of rheumatoid arthritis in man.

Not all workers were able to verify these results. Harrison (1946) and Pemberton, Eiman, Patterson, and Stackhous (1947) encountered arthritis in a group of rats on standard laboratory rations, in a group on grossly unbalanced diets, and in a group receiving large amounts of deoxycortone by injection. Pemberton and his associates were unable to show that thyroidectomy, adrenalectomy, or gonadectomy influenced the incidence or severity of the arthritis which took the form of focal areas of articular cartilaginous degeneration and ulceration. Many rats, they admitted, were heavily parasitized and controls were poorly defined. The published illustrations are unconvincing. Pirozynski and Akert (1949) repeated Selye's work. Among seventeen rats no spontaneous deaths occurred during the experiment; after 2 to 3 weeks fifteen showed a subacute non-suppurative focal polyarthritis. Controls were not used. Haour (1949) considered that the arthritic changes attributed to deoxycortone were not specific. The whole problem of the hormonal production of arthritis was discussed by Justin-Besançon, Rubens-Duval, Villiaumey, and Kahn (1953) in one of the few reviews of methods for the experimental study of arthritis. In their own work fifty rats were treated in accord-

Table IV

Experimental Production of Arthritis by Altered Endocrine Mechanisms

(1)	*Action of Deoxycortone Acetate in Normal Rats*	
	Selye and others	(1944)
	Harrison	(1946)
	Pemberton and others	(1947)
	Haour	(1949)
	Pirozynski and Akert	(1949)
	Justin-Besançon and others	(1953)
	Siebenmann and Uehlinger	(1953)
	Salgado	(1955)
	Smirnov and Beletskaia	(1955)
(2)	*Effect of Adrenal Damage in Deoxycortone Arthritis*	
	Harrison	(1951)
(3)	*Action of Deoxycortone in Adrenalectomized Rats*	
	Selye and others	(1944)
	Tarnopolsky and others	(1951)
(4)	*Action of Deoxycortone in Thyroidectomized Rats*	
	Selye and others	(1944)
	Pirozynski and Akert	(1949)
(5)	*Action of Deoxycortone in Thyroparathyroidectomized Rats*	
	Harrison and Barnett	(1953)
(6)	*Arthritis and the Influence of Cold in Adrenalectomized Rats*	
	Chamorro	(1945)
(7)	*Action of Pregneninolone in Adrenalectomized Rats*	
	Chamorro	(1945)
(8)	*Action of Adrenal Cortical and Anterior Pituitary Extracts in Castrated Thyroidectomized Rats*	
	Soto and Nava	(1950)
(9)	*Action of Stilboestrol Alone or with Cortisone*	
	Coutu	(1950; 1953)
	Jones and Carter	(1954)
(10)	*Hormonal Response to Parabiosis*	
	Hall and Hall	(1951)
(11)	*Action of Anterior Pituitary Hormones*	
	Bassi and Bassi	(1946)
	Soto and Nava	(1950)
	Selye	(1950a, b)
	Reinhardt and Li	(1953)
	Franz	(1957)
	Jasmin and Bois	(1959)
(12)	*Action of Somatotropic and Thyrotropic Hormones in Thyroidectomized Rats*	
	Salgado	(1955)
(13)	*Effects of Radiothyroidectomy in Mice*	
	Silberberg and Silberberg	(1954a, b)

ance with Selye's descriptions and they claimed to have produced a comparable arthritis. Their experiments remain open to criticism, but their review, with 107 references, is valuable. Siebenmann and Uehlinger (1953) agreed with Selye and others (1944) in attributing to deoxycortone and salt an inflammatory reaction, but they could not accept the implied analogy with human disease. Salgado (1955) referred to earlier work in which only two of 250 rats given deoxycortone developed arthritis detectable clinically, while of 100 rats given somatotrophin none developed arthritis. Smirnov and Beletskaia (1955) also found that deoxycortone alone was ineffective.

(2) Effect of Adrenal Damage in Deoxycortone Arthritis.—Harrison (1951) studied the production of arthritis in uninephrectomized rats given deoxycortone and salt. He showed that inadvertent damage to the arterial supply to the left adrenal could cause zonal necrosis, and suggested that this might account for the sensitizing influence of uninephrectomy in Selye's experiments through diminished secretion of glucocorticoids.

(3) Action of Deoxycortone in Adrenalectomized Rats.—The removal of the adrenals was considered by Selye and others (1944) and by Tarnopolsky, Schajowicz, Lustig, and Montuori (1951) to predispose to joint involvement in animals given deoxycortone, particularly during exposure to cold. However, adrenalectomy in the rat may be an uncertain procedure (Harrison, 1951).

(4) Action of Deoxycortone in Thyroidectomized Rats.—Selye and others (1944) and Pirozynski and Akert (1949) considered the influence of thyroidectomy on the evolution of the arthritis caused by deoxycortone. They agreed that thyroidectomy predisposed to arthritis but there was no indication whether this was a specific endocrine effect.

(5) Action of Deoxycortone in Thyroparathyroidectomized Rats.—Harrison and Barnett (1953) treated rats by thyroparathyroidectomy, with or without uninephrectomy. Five of the first group and three of the second developed arthritis within 33 days. There was, however, a high incidence of endemic infection in the colony and only thirteen animals survived to the end of the experiment. It is not possible to be certain that the lesions reported were similar to those of rheumatoid arthritis.

(6) Arthritis and the Influence of Cold in Adrenalectomized Rats.—Considered by Chamorro (1945).

(7) Action of Pregneninolone in Adrenalectomized Rats.—During work on pregneninolone, Chamorro (1945) observed the spontaneous development of arthritis in both treated and control groups among a series subjected to adrenalectomy. Because of the need for adrenalectomy he could not reconcile his findings with those of Selye. The number of animals studied was small.

(8) Action of Adrenal Cortical and Anterior Pituitary Extracts in Castrated Thyroidectomized Rats.—Soto and Nava (1950) were able to find articular swellings in eighteen of nineteen animals to which anterior pituitary and adrenal cortical extracts had been given following castration and thyroidectomy.

(9) Action of Stilboestrol Alone or with Cortisone.—Coutu (1950, 1953) studied four groups of adrenalectomized rats. To one group stilboestrol, to another cortisone, and to another both hormones were given. The extent of the arthritis was assessed by measuring limb diameters with calipers. Diethyl-stilboestrol was found, on this reckoning, to potentiate the effect of cortisone in inhibiting such a form of arthritis.

(10) Hormonal Response to Parabiosis.—In the course of a study of the "hypertensive hyalinosis syndrome", Hall and Hall (1951) noticed that many of the rats given salt to drink developed swollen joints. The swellings flitted unpredictably from joint to joint; small nodular lesions were found. In long-standing cases, cartilaginous erosion was added to synovial oedema and hydrarthrosis. To account for this response the currently acceptable theory of mineralocorticoid hyperfunction was advanced. This theory has not been substantiated. Incidental infection was not considered as a possible cause.

(11) Action of Anterior Pituitary Hormones.—Selye (1950a, b) produced an experimental arthritis resembling rheumatoid arthritis by the injection of freeze-dried material from anterior pituitaries. Reinhardt and Li (1953) compared twenty control animals with eighteen others from which the ovaries and adrenals had been removed and to which

freeze-dried pituitary extract had been given. Radiographs made after 6 months' treatment revealed joint erosions, localized osteoporosis, marginal lipping, and calcification. No histological evidence was adduced in this otherwise important paper; the authors conceded that sensitization to growth hormone had not been excluded as a cause of the arthritis. Nor was endemic infection considered. Franz (1957) quoted the work of Bassi and Bassi (1946a, b, c) in a study of acromegalic arthropathy, and Jasmin and Bois (1959) made similar claims for prolactin. Their illustrations show normal rat tissues.

(12) Action of Somatotropic and Thyrotropic Hormones in Thyroidectomized Rats.—Salgado (1955) showed that two of a group of animals given somatotropic hormone after thyroidectomy developed arthritis. By contrast no animals in a similar group given thyrotropic hormone developed such changes.

(13) Effects of Radiothyroidectomy in Mice.—Silberberg and Silberberg (1954a, b) showed that mice subjected to thyroid irradiation by ^{131}I developed articular lesions distinct from the degenerative joint disease found in ageing mice. In males, more susceptible than females, there was a strong positive correlation between the incidence of articular changes and that of hypophyseal tumours consequent on the thyroidectomy.

Comment

Few people now believe that the forms of arthritis induced by endocrine disturbances in small laboratory animals are strictly analogous with the arthritis of rheumatoid disease. It is possible that the extension of such studies to animal species more closely resembling man may prove more rewarding.

IV. Immunological Methods for the Experimental Production of Arthritis (Table V)

(1) Local Injection of Sensitized Animals with Serum.—A form of joint inflammation was produced by Friedberger (1913) after the aseptic injection of sterile homologous serum into the knee joints of sensitized rabbits. Unsensitized animals and those given heterologous serum showed no such response. To this early work an important stimulus was given by the reports of Klinge (1929, 1930, 1931, 1933), who demonstrated that the local injection of foreign serum into the limb joints of sensitized rabbits caused an acute inflammatory reaction in which fibrinoid change was prominent and which was followed by a proliferative arthritis resembling rheumatoid arthritis and by degenerative and deforming sequelae. Murasawa (1934), in somewhat different circumstances, found that horse serum given intravenously to rabbits caused no joint lesions, but Sonnenburg (1934) confirmed that an hyperergic serum arthritis developed in rabbits, particularly when injected joints were rested. Immobilization alone caused only local osteoporosis, but prolonged immobilization of the injected joint resulted in ankylosis. More and McLean (1949) sensitized rabbits with horse serum; repeated injections were given 17 to 18 days later. Only six of the 53 pairs of knee joints examined showed lesions more severe than those of control animals. By contrast, Ungar, Damgaard, and Weinstein (1951) injected guinea-pigs intravenously with anti-egg albumen serum, and followed this one hour later by a smaller local injection into the ankle joints. The degree of swelling, measured with a micrometer screw gauge, was proportional to the amount of antibody nitrogen injected. De Marchin (1952) was able to demonstrate an inhibitory influence of ACTH on the evolution of arthritis in guinea-pigs provided the hormone was given before the joints were injected. Similar studies were made by Cereser (1953). Again, Fassbender and Pippert (1954) sensitized rabbits with horse serum and showed that hyaluronidase exaggerated the resulting joint swelling, while intravenous rutin reduced it. Coburn and Haninger (1954) provided what they concluded was an experimental replica of rheumatic fever by the production, with rabbit anti-egg albumen serum, of the passive Arthus phenomenon in guinea-pigs. In a further paper (Coburn, Graham, and Haninger, 1954), it was demonstrated that egg white incorporated in the diet of young guinea-pigs afforded protection against the anaphylactic arthritis produced by the local Arthus phenomenon. Bocking and Brien (1955) compared immediate (anaphylactic) and delayed (bacterial) sensitivity in rabbits, contrasting the responses with those obtained with local injections of formalin or with blood. The lesions of rheumatoid arthritis, it was thought, were most closely simulated by delayed hypersensitivity responses. Strogonow (1956) also used the Arthus phenomenon to induce allergic arthritis in the rabbit. He considered that the central nervous system played an important role in this reaction, a view not generally accepted in laboratories where Pavlovian theory is not dominant.

TABLE V

IMMUNOLOGICAL METHODS FOR THE EXPERIMENTAL PRODUCTION OF ARTHRITIS

(1) *Local Injection of Sensitized Animals with Serum*	
Friedberger	(1913)
Klinge	(1929; 1930a, b, c; 1931; 1933)
Murasawa	(1934)
Sonnenburg	(1934)
More and McLean	(1949)
Ungar and others	(1951)
de Marchin	(1952)
Cereser	(1953)
Fassbender and Pippert	(1954)
Coburn and Haninger	(1954)
Coburn and others	(1954)
Bocking and Brien	(1955)
Strogonow	(1956)
(2) *Local Injection of Foreign Proteins Other than Serum*	
Gudzent	(1933)
Brunschwig and Henry	(1933)
Goldie	(1938)
Soeur	(1949)
Gardner	(1957a)
(3) *Injection of Homologous Tissues or of Adjuvants Alone*	
Cavelti	(1947)
Humphrey	(1948)
Peck and Thomas	(1948)
McKee and Swineford	(1951)
Glynn and Holborow	(1952)
Stoerk and others	(1954)
Boake and Muir	(1955)
Pearson	(1956)
Odell and Key	(1957)
Pearson and Wood	(1959)
(4) *Injection of Anti-Homologous Tissue Antisera*	
Favour and others	(1955)
(5) *Local followed by Systemic Injection of Antigenic Material*	
Faber	(1915)
Kinsella and Hagebush	(1929)
Moritz and Morley	(1931)
Brunschwig and Henry	(1933)
Angevine and others	(1942)
Morgan and Bennett	(1947)
(6) *Other Observations on Sensitization to Foreign Material*	
Angevine and others	(1942)
Jones and others	(1954)
(7) *Influence of Immunity on Infective Arthritis*	
Freundt	(1956a, b)

(2) Local Injection of Foreign Proteins Other than Serum.—Gudzent (1933) injected rabbits subcutaneously with food extracts of high protein content, and repeated the injections 8 to 10 days later. After 3 to 4 weeks, smaller amounts of the same extract were injected into the joints, and an inflammatory reaction appeared within 24 hours. Further injections caused a recurrence, but this was also sometimes spontaneous. Similar reactions were elicited with peptones prepared from animal proteins, novoprotein (of plant origin), and pyrifer (an extract of dead coliform bacilli). Gudzent concluded that this form of experimental arthritis was similar to certain forms of human rheumatism, which were likely therefore to have an origin in allergy to unknown proteins. Brunschwig and Henry (1933) injected rabbits intra-articularly with filtrates of *B. subtilis*, *Strept. viridans*, and diphtheria bacilli. When the animals were killed 24 hours later, the joint swellings were sterile. After 21 days there was synovial thickening with plasma-cell infiltration but no gross cartilaginous destruction. Egg white and human serum reacted similarly. Goldie (1938) confirmed Klinge's observations and caused a non-suppurative arthritis in rabbits by giving subcutaneous followed by intra-articular injections, using as antigen a suspension of ground-up haemolytic streptococci. Soeur (1949) made similar studies. Their conclusion, generally similar to that of Gardner (1957a) who used sterile human synovial fluid to inject guinea-pigs, was that a sustained arthritis could be produced by repeated injections of foreign protein, but that there was no satisfactory evidence of an allergic mechanism.

(3) Injection of Homologous Tissues or of Adjuvants Alone.—Among the most controversial aspects of the whole unsettled subject of experimental arthritis, are the reports dealing with the production of arthritis by the injection of homologous tissue, often with adjuvants designed to stimulate homologous tissue antibody formation (Freund, Casals, and Hosmer, 1937). The concept of sensitization to a homologous or autologous body tissue component, perhaps initiated by some incidental damaging factor, is a widely discussed, commonly quoted, and largely unsubstantiated hypothesis, which has been advanced to account for the pathogenesis of connective tissue disorders such as rheumatoid arthritis and systemic lupus erythematosus. The adoption of this hypothesis as a basis for the study of experimental arthritis may be traced to the work of Friedberger (1913), Masugi (1933), Klinge and Knapper (1935), Cavelti (1945, 1947, 1948), and Cavelti and Cavelti (1945a, b, c). Cavelti and Cavelti (1945a) put forward evidence to show that Group A β-haemolytic streptococci could render antigenic material obtained from the kidneys of an homologous organism. They described the production by this means of homologous tissue glomerulonephritis in the rat (Cavelti and Cavelti, 1945b, c), and of antibodies to heart, skeletal muscle, and connective tissue (Cavelti, 1947). This work, extensive and detailed, has not been confirmed. Indeed, Humphrey (1948) concluded that evidence for the production of such an anti-homologous kidney antibody was lacking. Peck and Thomas (1948), in equally thorough but negative work, injected 350 rabbits with homologous heart and kidney together with adjuvants from Group A and Group C β-haemolytic streptococci grown on protein-free media. In further unsuccessful work,

McKee and Swineford (1951) injected aseptic suspensions of joint and kidney tissue with washed, heat-killed streptococci. No anti-synovia antibodies or joint lesions were found. Glynn and Holborow (1952) were more successful in a limited experiment with heterologous chondroitin derived from human cartilage, but repetition of the almost identical experiment by Boake and Muir (1955) yielded no evidence of arthritis when rabbits were injected with homologous chondroitin and killed streptococci. The results of Glynn and Holborow were attributed to the presence in the antigen of traces of heterologous protein.

Renewed interest in the problem of producing an homologous tissue arthritis was aroused by the report of Stoerk, Bielinski, and Budzilovich (1954). These authors claimed to have produced a chronic polyarthritis in rats by injecting homologous spleen and adjuvants. Antibiotics did not influence the persistence of the lesions and repeated cultures grew no P.P.L.O. This work has not been confirmed. Somewhat similar experiments, repeated unsuccessfully by the reviewer, were described by Pearson (1956), who claimed to have produced joint and other lesions with injections of homologous muscle and adjuvants. This careful work was followed by an admission that similar joint lesions could be elicited by injecting Freund's adjuvants without muscle. Although P.P.L.O. had been recovered from several of the original animals, these organisms were not believed to be responsible for the arthritis (Pearson and Wood, 1959). Odell and Key (1957) used egg albumen as antigen with Freund's adjuvants in similar work in the rabbit; they confirmed that adjuvants alone caused a more severe arthritic reaction than when mixed with antigen.

(4) Injection of Anti-homologous Tissue Antisera.—Favour, Goldthwait, and Bayles (1955) reported the injection of cell-free saline extracts of guinea-pig synovia into rabbits. They subsequently injected into guinea-pigs the rabbit anti-guinea-pig synovia serum obtained in this way, after labelling with ^{131}I. No antibody localization in the joints was detected nor was there histological evidence of synovial lesions.

(5) Local Injection followed by Systemic Injection of Antigenic Material.—Faber (1915) described the injection of rabbit knee joints with killed streptococci; 14 to 65 days later a further, intravenous injection was made. Gross lesions developed only when additional intravenous injections were given. Kinsella and Hagebush (1929), using a freeze-dried preparation of streptococci in the same manner, produced an allergic arthritis. Moritz and Morley (1931) injected bacterial filtrates from *B. coli* and *B. typhosus* into rabbit knee joints, and cutaneous injections were given synchronously; 20 to 30 hours later intravenous injections of the same antigen were made. Six of eleven animals showed a synovial reaction, with endovascular damage, thrombosis, and vascular necrosis. Similar studies were made by Brunschwig and Henry (1933). Angevine, Cecil, and Rothbard (1942) considered that a previous intra-articular injection of killed streptococci or streptococcal nucleoprotein sensitized joints to a subsequent intravenous injection of homologous organisms, resulting in a more chronic reaction than occurred when the preliminary injection was intravenous or intradermal. Morgan and Bennett (1947) produced a chronic rabbit arthritis by repeatedly injecting extracts of the somatic antigen of the typhoid bacillus. As with the classical Schwartzman reaction, there was extensive local vascular damage with thrombosis and necrosis followed by repair.

(6) Other Observations on Sensitization to Foreign Material.—Jones, Carter, and Rankin (1954) emphasized that the capacity of a series of injections of the polysaccharides extracted from Friedlander's bacillus to cause joint changes was a measure neither of the anaphylactogenic nature of the extract, nor of its nitrogen or protein content. In the guinea-pig there was no correlation between the occurrence of cardiac or of joint lesions; the changes produced by mucopolysaccharides from various sources were non-specific.

(7) Influence of Immunity on Infective Arthritis.—In a series of experiments with *Streptobacillus moniliformis*, Freundt (1956a, b) showed that, while death occurred too quickly in non-immune groups for arthritis to develop, the joint inflammation appeared in a relatively high proportion of surviving immunized animals.

Comment

Disturbed immunological mechanisms in rheumatoid arthritis are suggested by several of the common characteristics of the disease. The location of gamma globulin and rheumatoid factor on synovial margins, for example, has been confirmed. Nevertheless, there is no direct evidence that rheumatoid arthritis is caused by a disorder of the immune mechanism, and it remains likely

that the serological criteria diagnostic of the disease are associated and not causal features.

In view of these points, it is doubtful whether any of the forms of experimental arthritis produced by the stimulation of immunological mechanisms bear any true relationship to the spontaneous disease. Like the varieties of arthritis induced by chemical and physical agencies, they retain some value in the testing of analgesic drugs, but it cannot be accepted that they have as yet thrown light on the pathogenesis of rheumatoid arthritis.

V. Physical Methods for the Experimental Production of Arthritis (Table VI)

The lack of clear distinction between the pathological changes in rheumatoid arthritis and those of degenerative joint disease, which prevailed until 1896 (Bannatyne, 1896, 1904) in spite of the considerably earlier definition of rheumatoid arthritis (Garrod, 1859), renders difficult the interpretation of many experiments employing physical agents. Many early workers attempted to reproduce degenerative joint disease (Pommer, 1915, 1929; Axhausen, 1913); more recently the use of physical agents has become common in experiments which have as their aim the reproduction of rheumatoid arthritis.

(1) Local Injection of Irritants.—Key (1929) injected adult rabbit joints with citrated blood or with India ink. The acute inflammatory reaction subsided within 12 days. He later claimed (Key, 1930) to have confirmed the experiments of Axhausen (1913), which suggested that degenerative joint disease followed cartilaginous necrosis, and those of Burckhardt (1924), in which immobilization of the damaged joint led to atrophic rather than to hypertrophic changes. Key concluded, after injecting the knee joints of guinea-pigs with carbolic acid, iodine, or alcohol, that the nature of the injected substance was not important provided damage was caused, and that this damage, if continued, would result in a deforming arthritis.

Coulon, Charlier, and Vandersmissen (1954) produced an experimental rat arthritis by the local injection of a 10 per cent. kaolin suspension. Cysteinamine was ineffective in treatment.

Comparable work by Ramsey and Key (1955), injecting 10 per cent. turpentine oil or talc in water, into the knee joints of 22 rabbits (using India ink as a guide to the sites of injection) showed that hydrocortisone accelerated the return of the damaged tissue to normal.

Table VI

PHYSICAL METHODS FOR THE EXPERIMENTAL PRODUCTION OF ARTHRITIS

(1) *Local Injection of Irritants*		
Blood, India ink, carbolic acid, iodine, alcohol	Key	(1929)
Kaolin	Coulon and others	(1954)
Turpentine, talc	Ramsey and Key	(1955)
Surgical sutures	Mannheim	(1929)
(2) *Local Cauterization*		
Heitzmann		(1874)
Mannheim		(1929)
(3) *Local Trauma*		
Redfern		(1850)
Sury		(1918)
Wehner		(1923)
Müller		(1924)
Mannheim		(1929)
Barthels		(1932)
Bich		(1932)
Bernstein		(1933)
Nozoe		(1938)
Magnuson		(1941)
(4) *Resection of Bone, Cartilage, or Synovia*		
Kroh		(1909)
Wehner		(1923)
Key		(1931)
Barthels		(1942)
Arnulf and others		(1954)
(5) *Local Electrolysis*		
Axhausen		(1913; 1914)
Mannheim		(1929)
(6) *Deprivation of Nerve Supply*		
Nozoe		(1938)
(7) *Local Cooling*		
Manteuffel		(1913)
Schiavetti and others		(1952)
(8) *Reduction in Blood Supply*		
Wollenberg		(1909)
Axhausen and Pels		(1911)
Walkhoff and others		(1911)
Goldhaft and others		(1930; 1933)
Bennett and Bauer		(1937)

According to Mannheim (1929), Billroth made comparable studies on the response of articular cartilage to the insertion of surgical sutures. A non-suppurative inflammation was induced.

(2) Local Cauterization.—Mannheim (1929) reported that Kremjanski (1868) cauterized the joints of the sternum and the ensiform cartilage of rabbits with a red-hot iron followed by the systemic administration of mercuric sulphide; 4 to 7 days later, fatty degeneration of the cartilage and cell destruction were found with mercuric salts in the perichondrium. From the same source we learn that Henzmer (1875) transfixed the capsules of rabbit hip joints with red-hot needles and cauterized the joints with zinc chloride. Neither pus formation nor cartilage cell proliferation followed. Heitzmann (1874) cauterized with red-hot irons the femoral condyles of rabbits, cats, and dogs. In the damaged areas he found cartilaginous calcification, cell degeneration, and an increased amount of interstitial ground substance.

(3) Local Trauma.—Redfern (1850) detailed the behaviour of cartilage cells in damaged joints. Much relevant work was quoted by Mannheim (1929), but often without the exact source. Sury (1918) compressed and distorted the knee joints of guinea-pigs several times weekly for 4 to 5 months. The joints of a further group he hit repeatedly with a hammer. Subsequent vascularization and ossification of the degenerate cartilage were found. Wehner (1923) rubbed and compressed the exposed articular cartilage while Müller (1924) produced epiphyseal displacement and femoral subluxation. By this means, and by arranging the tendons of the biceps to draw constantly across the head of the humerus he induced degenerative joint disease. Mannheim (1929) injected irritant fluids, and used both local bone destruction and prolonged local trauma to cause degenerative changes; he reported that Bonn had dislocated the radius, resected the capitellum or dislocated the radius, and fractured the ulna. In each instance changes resembling osteo-arthritis were found, and Bonn did not accept aseptic necrosis of cartilage as a prerequisite. Mannheim also reported that Schmidt had fractured the femoral epiphyses and then injected blood, concluding that cartilaginous destruction and arthritis were secondary to capillary damage, and that Billroth had made similar observations. Barthels (1932) performed synovectomy in rabbits, using the degenerative changes which appeared to support the contention that cartilage depends upon synovial fluid for normal metabolism. Bich (1932) combined traumatic dislocation and subluxation of the knee joints in rabbits with the subsequent injection of hydrochloric acid and studied the effect of alkalis on non-traumatized joints. Bernstein (1933) produced experimental arthritis in dogs by the exposure and ligation of lumbar veins, and Nozoe (1938) concluded that both local trauma and a metabolic disturbance were necessary factors in causing a neuropathic arthropathy. The work of Magnuson (1941) in dogs also emphasized a multiplicity of factors, including infection or chemical disturbance in addition to repeated trauma.

(4) Resection of Bone, Cartilage, or Synovia.—In a study of the pathogenesis of degenerative joint disease, Kroh (1909) resected part of the articular surface of rabbit femoral condyles and concluded that the disease developed following an incongruity in the joint surface. This view, unsubstantiated by histological evidence, neglects the observation that a fibrillary change in superficial articular cartilage is the earliest detectable histological lesion in this disease. The work of Wehner (1923) referred to above was followed by that of Key (1931), who also resected parts of the articular cartilages in twenty rabbits. His conclusions were similar to those of Kroh (1909). Unlike Axhausen (1913), he did not agree that the presence of a nidus of dead cartilage was necessary for degenerative changes to develop. Dead cartilage (he stated) placed in a joint is destroyed and removed without causing further damage. Barthels (1942) chose to excise the patella, and Arnulf, Benichoux, Desloux, and Morin (1954) used comparable methods in their study of the value of plastics in the treatment of chronic arthritis.

(5) Local Electrolysis.—Axhausen (1913, 1914) was the principal proponent of the value of electrolysis in the study of degenerative joint lesions. A current was applied to the articular surfaces; degenerative changes followed use of the joint. When a current of 2·5 milliamps alone was applied for 20 sec., aseptic cartilage and bone necrosis never occurred. Mannheim (1929) confirmed these observations.

(6) Deprivation of Nerve Supply.—Nozoe (1938) made a series of interesting observations on the relationship between joint integrity and nerve function. He deprived rabbit knee joints of their innervation by cutting lumbar segments 4 to 7 and sacral segments 1 to 2. The local injection of potassium permanganate then caused degenerative changes. Similar changes were induced by feeding 2 g. sucrose per kg. body weight daily. Nozoe concluded that local trauma, neuropathy, and a metabolic factor appeared to be necessary for the evolution of degenerative joint disease.

(7) Local Cooling.—Manteuffel (1913) approached the same problem by repeatedly cooling the lower legs of guinea-pigs by means of an ether spray. Vascular stasis was induced. Cartilaginous degeneration and an overgrowth of connective tissue followed. Schiavetti, Terzani, and Spitz (1952, contrasted the influence of cold and of trauma on the development of joint lesions in the rat and noted the effect of antibiotics.

(8) Reduction in Blood Supply.—It has always seemed likely that an alteration in the blood supply might explain the manner in which a noxious agent could cause arthritic lesions in rheumatoid arthritis as well as being an important accessory factor in the degenerative disease of elderly persons. Obliterative arterial disease near such joints is frequent, and the articular cartilage, dependent for its normal metabolism on the integrity of the synovia, is often the site of replacement fibrosis. Wollenberg (1909) was apparently the first to demonstrate joint changes

following a mechanical reduction in blood supply to the joint. Axhausen and Pels (1911) repeated Wollenburg's experiments, but concluded that the claim that an impaired blood supply was a factor in causing degenerative joint lesions was unjustified; they favoured the view that the presence of a nidus of necrotic cartilage was essential. Again, Goldhaft, Wright, and Pemberton (1930) claimed confirmation of the work of Wollenberg (1909). Degenerative and hypertrophic changes followed the occlusion of the patellar blood supply in dogs. Walkhoff Ewald, and Preiser (1911) repeated the same work in dogs and rabbits but with negative results. Goldhaft, Wright, and Pemberton (1933), in further studies, showed, not surprisingly, that the response of dogs to such procedures was conditioned by their maturity. Finally, Bennett and Bauer (1937) repeated these experiments yet again, this time with convincingly positive results.

Comment

Physical agents damaging to joints have been used experimentally to produce forms of arthritis which most frequently resemble degenerative joint disease in the human. There is no evidence that such methods lead to changes which by their nature or disposition resemble those of rheumatoid arthritis. The future elucidation of the nature and cause of rheumatoid arthritis is unlikely to result from methods of the kind mentioned in this section.

Summary

The cause of rheumatoid arthritis is not known. One of the reasons for this lack of understanding may be the absence of a true experimental replica of the disease. As part of an approach to this problem, a review has been made of the principal methods which have been described for producing arthritis experimentally. The methods, considered chronologically, have been divided for convenience into five groups: infective, chemical, endocrinological, immunological, and physical.

The conclusion is reached that none of the forms of experimental arthritis at present known bears more than a superficial similarity to rheumatoid arthritis in the human. It appears possible that this disease may be confined to man or to the primates. The suggestion is made that our understanding of the aetiology and pathogenesis of rheumatoid arthritis may be better advanced by a concentration of experiment on the organ and tissue responses in man and the anthropoid apes, than by a dissipation of effort on the laboratory study of arthritis induced in small rodents.

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Arthrite expérimentale

RÉSUMÉ

On ne connaît pas la cause de l'arthrite rheumatismale. Il est possible que cette méconnaissance serait due au fait qu'on n'ai jamais pu créer une copie expérimentale exacte de cette maladie. Comme une partie de l'approche à ce problème on passe en revue les principales méthodes décrites pour produire une arthrite expérimentale. Ces méthodes, considérées chronologiquement, ont été divisées, pour des raisons pratiques, en cinq groupes: infectif, chimique, endocrinologique, immunologique et physique.

On conclut que toutes les formes d'arthrite expérimentale connues à l'heure actuelle ne ressemblent à l'arthrite rhumatismale de l'homme que superficiellement. Il est bien possible que cette maladie soit limitée à l'hombre ou aux primates. On suggère que nos connaissances de l'étiologie et de la pathogénie de l'arthrite rhumatismale avancerait mieux si l'on concentrait l'expérimentation sur des réactions des tissus et des organes humains et anthropoïdes plutôt que dissiper des efforts en l'étude de laboratoire de l'arthrite provoquée chez des petits rodents.

Artritis experimental

SUMARIO

La causa de la artritis es desconocida. Una de las razones de este desconocimiento puede ser la falta de una verdadera reproducción experimental de la enfermedad. Como una parte en el estudio de este problema, se pasa revista a los principales métodos descritos para la producción experimental de la artritis. Dichos métodos, considerados cronológicamente, fueron divididos por conveniencia en cinco grupos: infectivos, químicos, endocrinológicos, imunológicos y físicos.

Se concluye que ninguna de las formas de artritis experimental conocidas en el momento presenta con la artritis reumatoide en el hombre más que una similitud superficial. Parece posible que esta enfermedad se limita al hombre o a los primates. Se sugiere que el conocimiento de la etiologia y patogenia de la artritis reumatoide puede avanzar más por una concentración de experimentos sobre la respuesta de organos y tejidos en el hombre y monos antropoides que con una dispersión de esfuerzos en el estudio en el laboratorio de la artritis producida en pequeños rodentes.

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SULPHATE ($^{35}SO_4$) UPTAKE BY CHONDROCYTES IN RELATION TO HISTOLOGICAL CHANGES IN OSTEO-ARTHRITIC HUMAN ARTICULAR CARTILAGE

BY

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Quantitative studies of sulphate uptake by the cells of human cartilage (McElligott and Collins, 1960) have shown that chondrocyte activity increases in articular cartilage as age advances, while it decreases in costal cartilage. A considerably enhanced activity of articular over costal cartilage cells was recorded in cases where there was naked-eye evidence of destruction and fibrillation of the articular cartilage. We postulated a possible relationship between the increased sulphate utilization of ageing articular cartilage, the degree of osteo-arthritis, and the peculiar rearrangement and grouping of chondrocytes that are known to occur in these conditions. In order to investigate this, a large number of autoradiographs of cartilage incubated with labelled sulphate have been prepared and studied side by side with parallel sections stained by various methods including those that demonstrate mucopolysaccharides. It is the results of these studies that we now report.

Material and Methods

A patella was removed at each of 34 necropsies from persons ranging in age from 4 to 83 years. Specimens were processed as soon as possible after removal and in all cases within 2 hours. During this delay the specimens were stored at 4° C. in the incubation medium, a procedure that reduces the rate of loss of chondrocyte activity. The intervals between death and autopsy and between the collection of the specimen and its processing were carefully noted.

Preparation of Specimens.—The patellae were inspected and changes of osteo-arthritis, if present, were graded 0-4 according to the classification proposed by Collins (1949, p. 76). Blocks of cartilage down to the bone were removed from the complete transverse diameter of the patellae and processed for quantitative measurement of sulphate fixation in 31 cases, as previously described (McElligott and Collins, 1960).

Another block of cartilage with its subjacent bone was then cut from the specimen; this second block of cartilage adjoining that removed for radiochemical assay was used for the histological procedures to be described. The cut surfaces of the cartilage were then shaved with a razor so as to produce a block of the complete depth of the articular cartilage 1 mm. or less in thickness resting on a broader supporting block of the underlying bone, since thicknesses of cartilage greater than 1 mm. impair the uptake of $^{35}SO_4$ (Boström and Månsson, 1953).

Incubation Medium.—The medium used for incubating the specimens and in which they were transported was that described by Kodicek and Loewi (1955). It is a salt solution containing glucose buffered to pH 7·3. For quantitative estimations of sulphate fixation, sulphate as sodium sulphate 4·8 mg. per litre was added. In the preparation of autoradiographs no sulphate was added as carrier, as Layton (1950) reports that higher uptake of radioactive sulphate occurs where carrier is omitted.

Radiochemical Technique.—The *quantitative procedure*, based on the methods fully set out by Layton (1949, 1950) and by Kodicek and Loewi (1955), has been previously described (McElligott and Collins, 1960). In the *preparation of autoradiographs* the blocks of cartilage and bone were incubated in 10 ml. medium at 37° C. in a water bath, in flasks mounted in a mechanical rocker. Approximately 5 microcuries (μc.) of ^{35}S per ml. (carrier-free sulphate supplied by Radiochemical Centre, Amersham) was added to the incubation medium.

After 4 hours incubation, the blocks were rinsed with ice-cold isotonic (2·5 per cent.) sodium sulphate and fixed in 10 per cent. neutral formalin. After decalcification, dehydration, and double embedding by Peterfi's method, sections were cut at 7μ.

Autoradiographs were prepared by the stripping film technique of Doniach and Pelc (1950) using Kodak A.R.10 film. The preparations were exposed in the dark in a refrigerator, generally for 60 days. Some sections were stained before mounting by the periodic acid-Schiff (P.A.S.) technique; others were stained with 1 per cent. safranin through the overlying film after exposure and development.

Histological Methods.—Serial sections were stained in the following order:

(1) Ehrlich's acid haematoxylin and eosin.
(2) Periodic acid-Schiff (P.A.S.) omitting the bisulphite rinse (Gomori, 1952).
(3) Alcian blue (Zugibe, Brown, and Last, 1959).
(4) Phosphotungstic acid haematoxylin (P.T.A.H.).
(5) Van Gieson's stain with Weigert's iron haematoxylin.
(6) Laidlaw's silver carbonate method for reticulin (Laidlaw, 1929).
(7) Toluidine blue for metachromasia, the stained and rinsed sections being fan-dried before clearing and mounting.

Explanation of Terms.—Reference will repeatedly be made to Articular Cartilage Zones 1-4 and Osteo-Arthritis Grades 0-4. These terms must therefore be clearly defined.

CARTILAGE ZONES.—Basing his observations on those of Benninghoff (1925), Collins (1949, p. 22) recognized four strata in normal human articular cartilage, not only by the position of the collagen fibres but also by the character of the cells, *viz.*:

Zone 1 Superficial; numerous small cells, fibres arranged tangentially.
Zone 2 Transitional; cells moderately large and equally spaced, fibres pursuing an oblique course and interlacing.
Zone 3 Deep; larger cells, often in groups of four to eight, in rows between radially arranged parallel fibres.
Zone 4 Calcified zone adjacent to bone; lying beneath the wavy basophilic line identifiable in decalcified sections of every adult bone end and appropriately termed the "tide-mark" by Fawns and Landells (1953).

GRADES OF OSTEO-ARTHRITIS.—This pathological grading of the cartilage and bone changes of age and osteo-arthritis was fully described by Collins (1949, p. 76). In summary, the principal distinguishing features of each grade are as follows:

Grade 0 Normal healthy joint with smooth cartilage.
Grade I Superficial flaking of cartilage in areas of pressure and movement.
Grade II More extensive destruction of cartilage not denuding bone.
Grade III Total loss of cartilage in one or more pressure areas and obvious marginal osteophytes.
Grade IV Complete loss of cartilage from large areas with eburnation of bone; prominent osteophytes.

This scheme of grading depends on naked-eye assessment. The extent of cartilage destruction may vary from area to area, but changes that fairly represent each grade are described and illustrated in what follows.

Results

The results fall into two sections:

(*a*) The quantitative results of radio-assay, which indicate the over-all avidity for sulphate displayed by all the chondrocytes in the sample of cartilage;
(*b*) The results of our study of histological sections and their autoradiographs, from which we can deduce the behaviour of individual chondrocytes or clusters of chondrocytes in relation to the different zones of cartilage and to the general matrix under varying conditions of cartilage injury and disintegration.

A total of 34 patellae from 34 different persons provided histological material (Table I). Quantitative assays of sulphate utilization *in vitro* were made in 31 cases. Sex made no difference to the results; increasing grades of osteo-arthritis tended to occur with increasing age, but individual variation in this respect was considerable.

TABLE I

SUMMARY OF MATERIAL EXAMINED QUANTITATIVELY AND HISTOLOGICALLY

Grade of Osteo-Arthritis	Total No. of Cases (each fully studied histologically)	Age Range (yrs)	No. quantitatively Assayed
0	4	4–35	4
I	12	20–75	11
II	10	44–75	10
III and IV	8	68–83	6
Totals ..	34	4–83	31

Quantitative Results.—These show increased sulphate utilization by the chondrocytes in the more severe grades of osteo-arthritis (Table II).

TABLE II

UPTAKE OF SULPHATE BY PATELLAR ARTICULAR CARTILAGE *IN VITRO* (μg. SO_4/g. DRIED CARTILAGE) 31 NECROPSIES IN WHICH VARYING GRADES OF OSTEO-ARTHRITIS WERE ENCOUNTERED

Grade of Osteo-Arthritis	No. of Specimens	SO_4 Uptake (μg./g.)	
		Mean	Range
0	4	0·18	0·12 to 0·29
I	11	0·56	0·14 to 1·0
II	10	0·80	0·35 to 1·89
III and IV	6	1·04	0·49 to 1·72

Quantitative results in individual cases are not closely related to the recorded grade of more advanced osteo-arthritis. Sulphate uptake clearly depends to some measure on the particular area sampled; a slice that includes much totally exposed bone, for example, would obviously contain few functioning chondrocytes.

The ages of the patients have not been included in Table II. Sulphate utilization in articular cartilage, but not in costal cartilage, tends to increase with age, but this is probably due to the structural changes of osteo-arthritic pattern that commonly develop in the elderly knee joint, since age causes a diminution of chondrocyte activity in costal cartilage. Figures previously published (McElligott and Collins, 1960) show that the degree of osteo-arthritis is more important than age alone in increasing the ratio of activity between articular and costal cartilage. Furthermore, investigations now in hand (Meachim and Collins, to be published) indicate that mere ageing of the articular cartilage of a joint that is not subject to osteo-arthritis is not associated with increased sulphate utilization.

Histological and Autoradiographic Results

Grade 0.—In normal articular cartilage the chondrocytes are fairly evenly distributed though varying somewhat in size and tending to lie in small clusters in Zone 3. In children, all staining reactions, basophilia with acid haematoxylin, metachromasia, P.A.S., and alcian blue, are evenly intense throughout the thickness of cartilage. In adults the staining of the superficial layer (Zone 1) becomes weaker. P.A.S. staining remains in the deeper part of Zone 3 and as collars around the cells in Zone 4 (Fig. 1). Metachromasia, basophilia, and alcian-blue staining tend to fade from the deep Zone 3 though remaining strong in upper Zone 3, forming pools of colour around the chondrocytes (Fig. 2) and in Zone 2 where the staining is often quite diffuse. These observations agree in the main with those of Fawns and Landells (1953), who rightly point out that in older people the matrix towards the basal zone becomes eosinophilic in the ordinary haematoxylin and eosin stain, though the included cells remain strongly basophil and metachromatic.

The autoradiographs reveal an intense image over the cells in Zones 2 and 3. The smaller cells of Zone 1 are feebly active or inactive (Fig. 3, opposite) and this confirms what the ordinary section (Fig. 4, opposite) suggests, that these superficial cells are effete. The cells in Zone 4 generally show no uptake of sulphate, although surrounded by a P.A.S.-positive collar (Fig. 5, opposite).

The autoradiographic picture of human articular cartilage after sulphate ($^{35}SO_4$) incubation has not hitherto been described, so far as we are aware. Our results show that in undamaged cartilage all the cells in Zones 2 and 3, that is, in at least four-fifths of the cartilage depth, are actively synthesizing sulphated mucopolysaccharides (chondroitin),

Fig. 1.—Normal patellar cartilage (Grade 0) from a man aged 35. Strong P.A.S. reaction in Zone 3 and P.A.S.-positive collars around cells in the calcified Zone 4 adjoining the bone. (J.24) P.A.S. × 125.

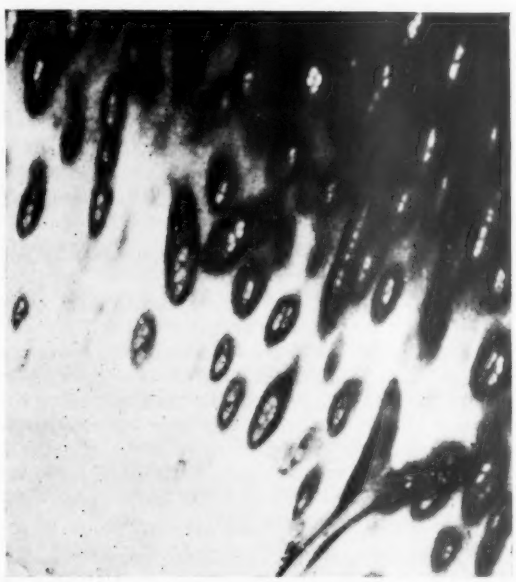

Fig. 2.—Normal patellar cartilage (Grade 0). Strong staining around chondrocytes in upper Zone 3 and more diffusely in Zone 2. (J.24) Alcian blue × 50.

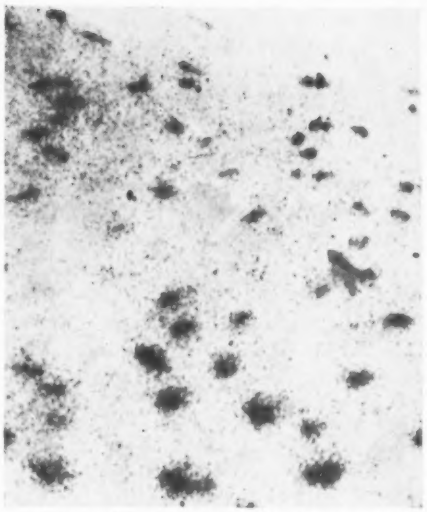

Fig. 3.—Normal patellar cartilage (Grade 0). Autoradiograph showing sulphate uptake by chondrocytes in Zone 2, but little in the superficial Zone 1. (J.24) × 125.

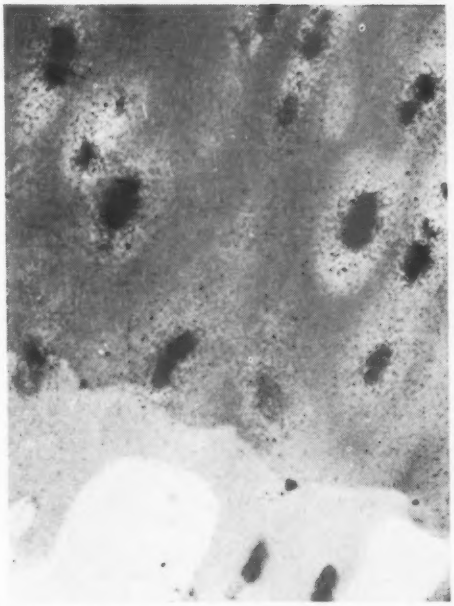

Fig. 5.—Normal adult patellar cartilage. Autoradiograph with P.A.S. stain shows diffuse P.A.S. reaction in Zone 3, except around the very active chondrocytes, and weak P.A.S. reaction in Zone 4, except for collars around the chondrocytes which here show no sulphate fixation. (J.24) P.A.S. × 125.

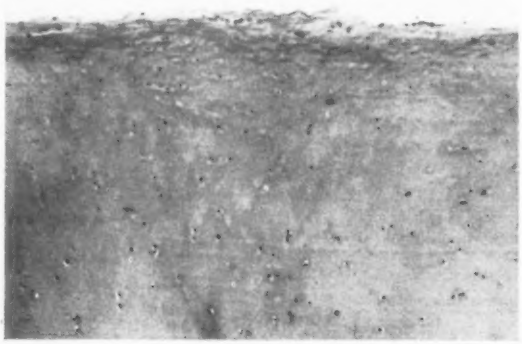

Fig. 4.—Normal patellar cartilage (Grade 0) from a boy aged 14. Diffusely positive P.A.S. staining. Small effete cells in superficial Zone 1 which shows an insignificant amount of flaking. (J.9) P.A.S. × 50.

whereas this function tends to be lost by the effete cells of the superficial Zone 1 and by those cells that have become interred in the calcified Zone 4.

Grade I.—Histologically, the cartilage here shows tangential flaking of the superficial Zone 1 (Fig. 6).

In some of the twelve specimens included in this group, destruction of cartilage had advanced to the extent of vertical or oblique fibrillation of Zone 2

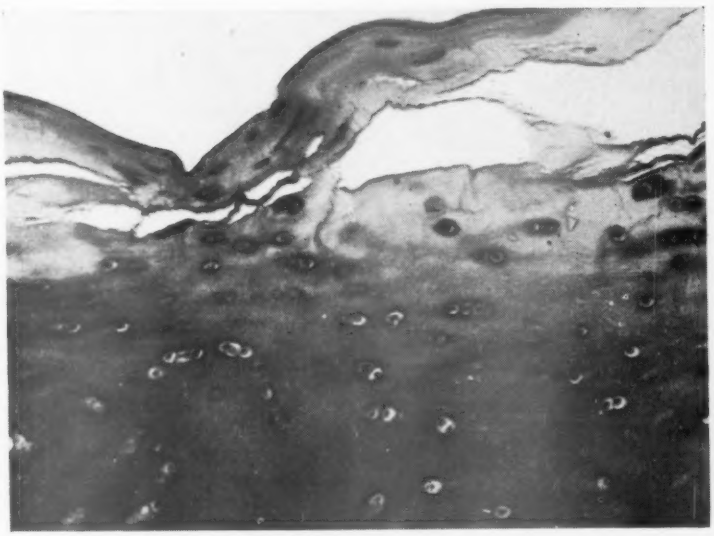

Fig. 6.—Patellar cartilage showing Grade I changes. Tangential flaking of surface (Zone 1). Loss of P.A.S. reaction in the matrix and of chondrocytes in this zone. (J.6) P.A.S. × 125.

(Fig. 7), but never more deeply. The normally effete cells of Zone 1 are not stimulated to activity when tangential flaking occurs. They tend to disappear even before the flakes of matrix separate (Fig. 6), and the autoradiograph shows no increased fixation of sulphate by any of the cells of the cartilage, provided that fibrillation is restricted to Zone 1 (Fig. 8). When, however, the cracks in the fibrillated cartilage reach obliquely into Zone 2 and begin to fibrillate vertically, reactive cell clumps appear (Fig. 7), and these demonstrate enhanced radioactivity through sulphate fixation. This is not a general feature in the specimens that fall within this grade, since most cartilages showing deep vertical fibrillation come to be graded as II or III. The section of one patella (J.16) that to the naked-eye revealed no more than Grade I changes

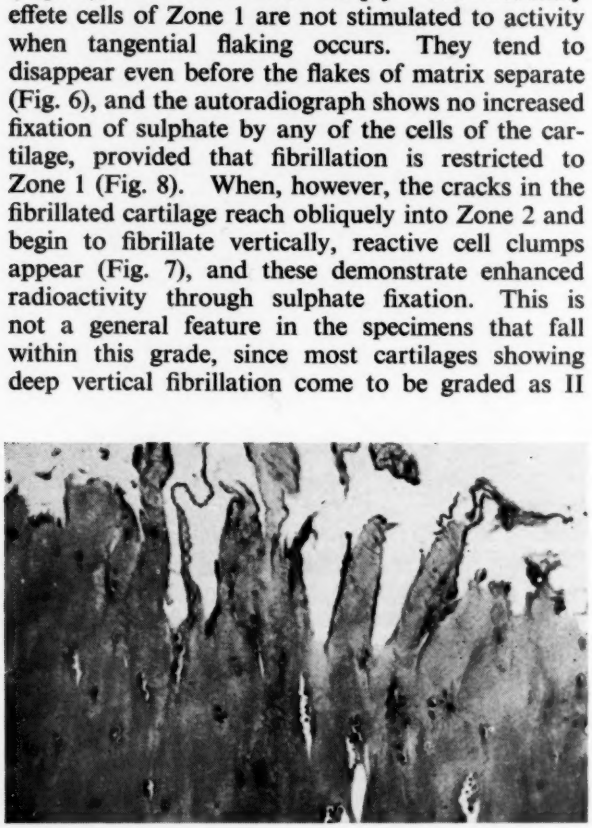

Fig. 7.—Patellar cartilage showing Grade I changes, here including shallow fibrillation of Zone 2; the tangentially flaked fragments of Zone 1 have mostly become detached. Small clumps of chondrocytes appear. (J.3) P.A.S. × 50.

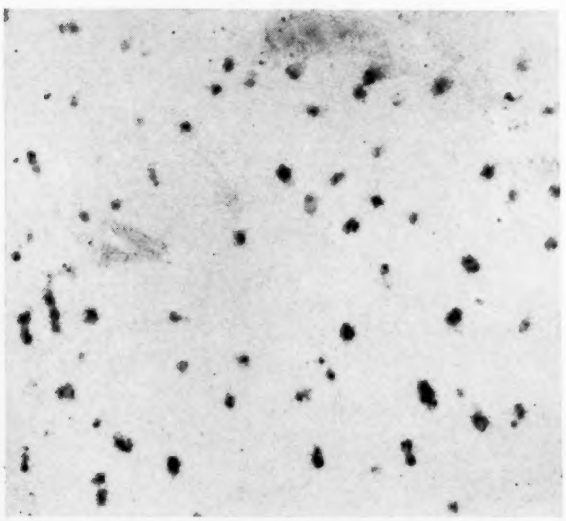

Fig. 8.—Grade I. Autoradiograph showing poor uptake of sulphate by the cells of the broken up superficial Zone 1 as compared with still normal chondrocytes in deeper Zones 2 and 3. (J.21) × 125.

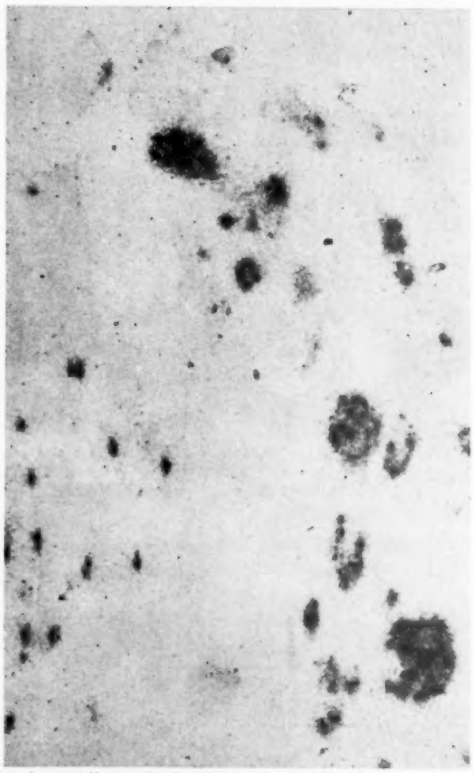

Fig. 9.—Autoradiograph showing a single deep fissure, with fracture of the subchondral bony plate, in a cartilage showing elsewhere only Grade I changes. The chondrocytes of Zones 2 and 3 have here formed large clumps and show active sulphate fixation. (J.16) × 125.

Fig. 10.—Grade I. Fibrillation extending into the transitional oblique-fibred Zone 2. The general matrix in the fibrillated area fails to stain metachromatically and appears colourless when photographed through an orange filter. (J.10) Toluidine blue × 50.

happened to include a fracture through the cartilage and the subchondral plate, beneath which was a focus of reparative fibrosis. This single deep fissure, almost certainly originating from a specific, though unspecified, injury, was bordered by large clumps of very actively functioning chondrocytes (Fig. 9). P.A.S. staining reactions accord with their distribution in normal cartilage. The most strikingly abnormal histochemical reaction seen was the loss of metachromasia in the normally positive Zone 2 when this becomes fibrillated (Fig. 10, opposite). It is the general matrix of this zone that now stains orthochromatically; metachromasia is still seen around the proliferated and sulphate-fixing chondrocyte groups.

Grade II.—In this group the usual cartilage changes are the total loss of Zone 1, a fringe of tags surviving from Zone 2, and vertical fibrillation causing clefts between the radial fibre lines of Zone 3. The clefts do not generally extend to the base of Zone 3; when this happens blocks of cartilage are liable to break off from their calcified or bony base and this constitutes a Grade III event.

The chondrocytes of Zones 2 and 3 are viable cells that respond to the breaking up and apparent leaching away of matrix by multiplication and the formation of cell clusters in which twenty or more nuclei may be counted (Fig. 11). These cell groups are very active in fixing sulphate and an intense autoradiographic image forms over them (Fig. 12).

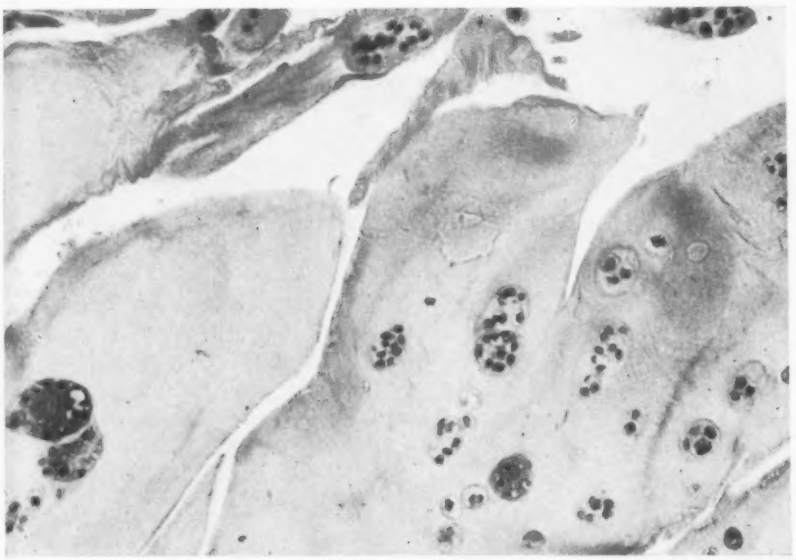

Fig. 11.—Grade II. Clumps of proliferated and viable chondrocytes in fibrillated area of Zone 2. The outlying matrix has lost its basophilia. (J.26) Haematoxylin and eosin × 125.

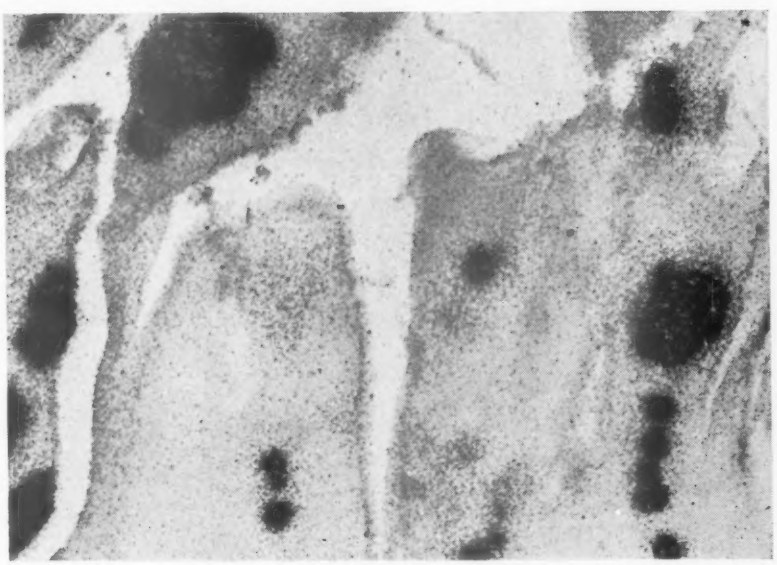

Fig. 12.—Grade II. Autoradiograph showing fibrillation of cartilage Zones 2 and 3, and intense image over the large cell clusters shown in Fig. 11. (J.26) × 125.

The same cells show strong metachromatic reaction with toluidine blue, which is most strong over the cell clusters but also lightly diffused around them (Fig. 13).

Fig. 13.—Grade II. Strong metachromasia of cell clumps in fibrillated cartilage of Zones 2 and 3. (J.28) Toluidine blue with orange filter × 125.

A strong metachromasia is also seen around the cell groups in the more deeply fibrillated zone (Fig. 14).

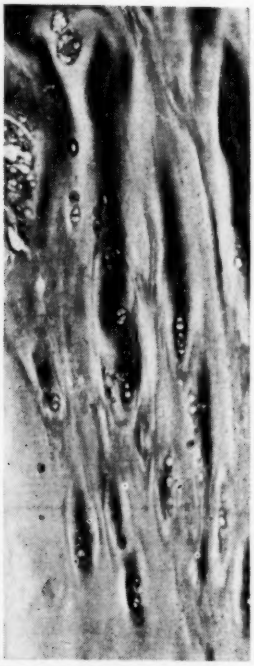

Fig. 14.—Grade II. Metachromasia over and in the vicinity of chondrocytes in the deeper fibrillation of Zone 3 cartilage. (J.32) Toluidine blue with orange filter × 50.

Alcian-blue staining follows exactly the same pattern of distribution as metachromasia, and metachromasia and intense alcian-blue staining are localized within and around cell groups that always show intense autoradiographic images. It is to be deduced therefore that these two histochemical reactions occur where sulphated mucopolysaccharides are being synthesized.

The P.A.S. reaction, however, is distributed in an inverse manner. When the autoradiographic section is stained P.A.S., the sulphate-fixing chondrocytes are seen to lie within a halo of unstaining matrix, although the intervening matrix, further removed from the cell groups, is P.A.S. positive (Fig. 15). This finding is the corollary of the observation already illustrated in Figs 1 and 5, that the chondrocytes of Zone 4 are generally surrounded by a collar of P.A.S. material but are inactive in sulphate utilization.

Fig. 15.—Grade II. Autoradiograph showing fibrillation extending through Zone 2 to Zone 3. All chondrocytes show sulphate fixation, well marked in the fibrillated areas. Each group of these actively sulphating cells is surrounded by a halo of P.A.S.-negative material. Note also that P.A.S.-positive material tends to remain in the superficial tags of Zone 2. (J.32) P.A.S. × 50.

Grades III and IV.—The division between Grades III and IV of osteo-arthritis is based on the naked-

eye appearances of the joint. Microscopy of small areas of cartilage does not distinguish between them. In both grades, cartilage destruction somewhere has proceeded to total loss of the uncalcified cartilage of Zones 1 to 3 and denudation of bone, perhaps, incorporating some residues of the calcified cartilage of Zone 4 (Fig. 16).

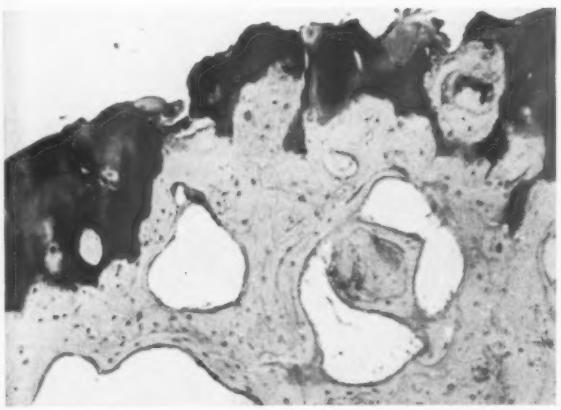

Fig. 16.—Grades III and IV. Total loss of uncalcified articular cartilage giving the gross appearance of a bared bone end, though islands of Zone 4 calcified cartilage often remain, shown here to give a certain metachromatic reaction. (J.30) Toluidine blue × 50

The main strata of cartilage seem at this stage of disintegration to have been shorn off along the "tide-mark" line that normally separates Zones 3 and 4. Later this denuded bone may become still further worn down and compacted like ivory

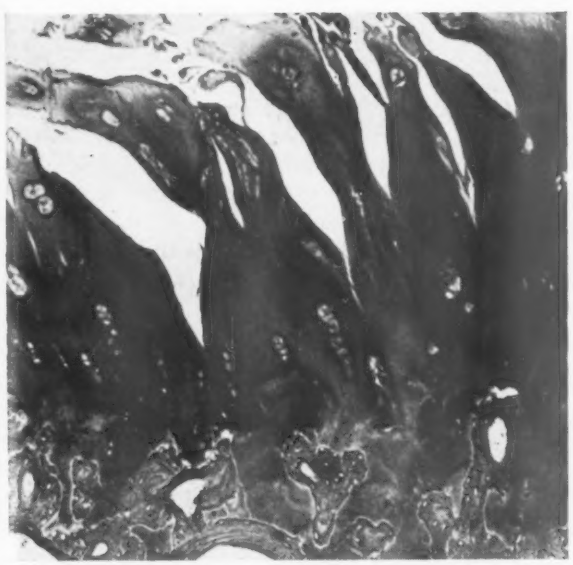

Fig. 17.—Grades III and IV. Vertical fibrillation of Zone 3 cartilage extending as deeply as Zone 4 and the underlying bone. (J.30) Reticulin stain × 50.

(eburnation) as a result of apposition of new lamellar bone upon the subchondral trabeculae. Eventually most of the Zone 4 cartilage is worn away.

Apart from denudation of bone, the principal cartilage change in Grades III and IV is vertical fibrillation through the deepest part of Zone 3 (Fig. 17). At this stage all of Zone 1 cartilage and most of Zone 2 has already been lost.

Chondrocytes proliferate to form huge clusters of cells in the fibrillated Zone 3 (Fig. 18).

Fig. 18.—Grades III and IV. Large clusters of chondrocytes in fibrillated cartilage of Zone 3. P.A.S.-negative reaction around these cell groups. (J.31) P.A.S. × 50.

P.A.S.-positive material fades from the matrix immediately surrounding these cell groups. Metachromatic material is, however, concentrated around the cartilage cells and in the matrix immediately surrounding the cell clusters (Fig. 19, overleaf), and alcian-blue staining is similarly distributed. The same cells are shown by autoradiography to be very active users of sulphate (Fig. 20, overleaf). Under higher magnification the autoradiographs show very clearly that the uptake of sulphate is localized to the cell groups and often to individual cells within the group (Fig. 21, overleaf).

Some sections gave us the opportunity to study the junction between surviving cartilage and denuded bone. The deeply fibrillated Zone 3 loses more and more of its thickness and tapers down

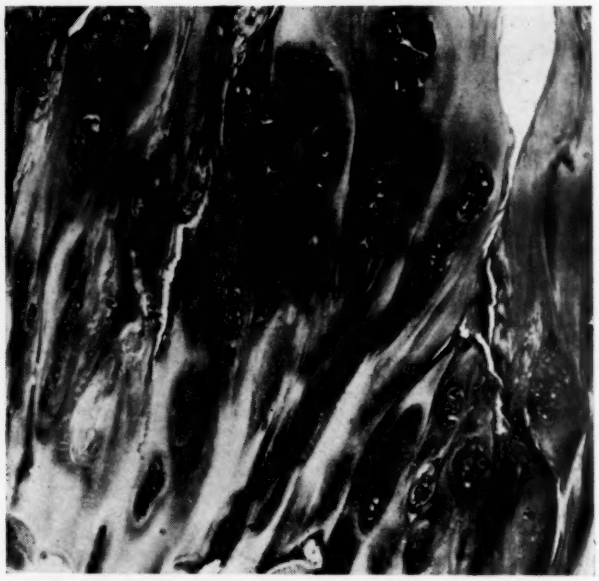

Fig. 19.—Grades III and IV. Strong metachromasia over and around chondrocyte clusters in fibrillated cartilage of Zone 3. (J.31) Toluidine blue × 50.

Fig. 20.—Grades III and IV. Autoradiograph of fibrillated cartilage in Zone 3 showing great activity of chondrocytes in fixing sulphate. (J.31) × 50.

towards the denuded region, but the chondrocytes are still active and viable, forming the usual large clumps that seem to be their response to fibrillation and loss of matrix, and they still show active sulphate utilization in the autoradiographs and the elaboration of material that stains well with alcian blue and is strongly metachromatic (Fig. 22, opposite).

The final disintegration of the cartilage seems to result from the development of horizontal clefts that meet with the vertical clefts in the fibrillated Zone 3 and cause small masses of cartilage to

Fig. 21.—Grades III and IV. Autoradiograph magnified to show localization of image over cell groups and over individual cells within the group, clearly indicating that sulphate fixation during *in vitro* incubation of cartilage is a vital function of chondrocytes. (J.35) × 125.

crumble away. The horizontal cleavage generally takes place along or close to the tidemark line that is the upper boundary of the calcified cartilage of Zone 4.

A noteworthy feature, well seen in sections stained for reticulin (Fig. 23, opposite), is the withering up of the tags of cartilage when they are nearly isolated from the main mass of cartilage. It seems that the mucopolysaccharide matrix dissolves away, leaving contracted spirals of collagen fibre bundles. In many such situations the chondrocytes within the shrinking tags still show intact nuclei, metachromasia, and sulphate fixation; but sometimes before the fragment of decadent cartilage finally separates the cells seem to die.

Discussion

It has been our aim to illustrate in some detail the cellular changes that develop in articular cartilage as it breaks up and wears away on a joint surface, and to relate these changes in the cells with their capacity for synthesizing sulphated mucopolysaccharides and with the histochemical reactions of the surrounding cartilage matrix.

The disintegration of cartilage so commonly seen in ageing joints that are exposed to trauma,

Fig. 22.—Grades III and IV. Progressive loss of depth of fibrillated Zone 3 at edge of denuded area (to right). Chondrocyte clumps are very large and the cells continue to elaborate metachromatic (dark) material. (J.35) Toluidine blue × 125.

Fig. 23.—Grades III and IV. Disintegration of articular cartilage at the edge of an area of denuded bone (right). Cell clumps still survive in many of the tags, but the amorphous mucopolysaccharide matrix is being lost to expose contracted spirals and wavy outlines of collagen fibre bundles. (J.30) Reticulin stain × 50.

such as the articulation of the patella which we chose for our material, is often referred to as a degeneration and it is known to lead to osteo-arthritis, or, as it is often termed, degenerative arthritis. But we have already shown, by quantitatively comparing the trend of sulphate utilization with age (McElligott and Collins, 1960), that the cells of ageing patellar cartilage show an enhanced capacity to synthesize chondroitin sulphate and, therefore, that osteo-arthritis is not due to a loss of function of the chondrocytes. The anomaly this presented was the revelation that, though we know that there is a loss of substance and a disintegration of articular cartilage in osteo-arthritis, the cells that remain are much more than normally capable of utilizing sulphate, which, for reasons fully explained in our earlier paper, is a measure of the rate of synthesis of sulphated mucopolysaccharide. We thought at that time that there might be a relationship between the enhanced sulphate utilization in ageing articular cartilage, the degree of osteo-arthritis, and the peculiar rearrangement and grouping of chondrocytes that are seen in the conventional histological section of the osteo-arthritic cartilage. Our present studies show that this is indeed the case.

Table II, which is based on quantitative results obtained mostly before our earlier paper and used there for a comparative study with costal cartilage, shows that increasing degrees of osteo-arthritis lead to increasing uptake of labelled sulphate *in vitro*.

The grades of osteo-arthritis of which we speak are pathological grades. They do not correspond to any clinical grade. They relate only to a single articular surface, that of one patella, and what we have called Grades I and II of osteo-arthritis are most likely to be sub-clinical lesions. No objection can be taken to this, because sub-clinical grades of other disease processes, discoverable only by the pathologist, are very generally recognized. Some may quibble that these are grades of "age change"

and not of osteo-arthritis, but from our parallel studies on costal cartilage, already published, and from our studies of weight-bearing and non-weight-bearing joint surfaces which are still being pursued, we are convinced that the changes outlined in an earlier part of this paper are to be classified only as those of osteo-arthritis.

Autoradiographs clearly show that the increased utilization of sulphate by osteo-arthritic cartilage is a function of the chondrocytes, and especially of those chondrocytes that proliferate to form multicellular clusters in the fibrillated areas of Zone 3 and, to a somewhat less extent of Zone 2. The chondrocytes of superficial Zone 1 in normal cartilage have the appearance of biologically effete cells and fix little or no sulphate; they do not react to the destruction of cartilage by tangential flaking that is seen in the earliest (Grade I) lesion of osteo-arthritis.

Curran and Gibson (1956) state that the isotope technique for estimating sulphate fixation in cartilage is a test of the viability of cartilage cells, and the application of the method to osteo-arthritic articular cartilage has proved that in such cartilage the cells are not dead or functionally inactive. On the contrary, their capacity for synthesizing chondroitin sulphate seems to be stimulated. It seems reasonable to suppose that the cells react in this way to the breaking up and loss of the surrounding cartilage matrix, but whether this is caused by mechanical trauma, by enzymatic action, or by other means is a point on which our present studies offer no evidence.

Experiments involving the depletion of living cartilage matrix by papain are relevant to this matter. Thomas (1956) originally observed that the ears of rabbits injected intravenously with crude papain flopped, and he discovered that this was due to a loss of the mucopolysaccharide matrix. Subsequent work showed that papain a ected many other cartilages in the rabbit and that the breaking down of chondro-mucoprotein releases large amounts of chondroitin sulphate into the circulation (Bryant, Leder, and Stetten, 1958; Tsaltas, 1958; Weissmann, Potter, McCluskey, and Schubert, 1959). Quantitative studies with ^{35}S on the costal cartilages of papain-treated rabbits have very recently shown that the depletion of matrix brought about by this enzyme stimulates the chondrocytes to enhanced activity in synthesizing chondroitin sulphate (McElligott and Potter, 1960). This finding strongly supports our view that it is loss of matrix that primarily stimulates the cells in osteo-arthritic cartilage.

The large cell clusters of osteo-arthritic cartilage almost certainly form by the proliferation, and not by the mere aggregation, of existing chondrocytes. That we have never, in many scores of sections, seen the mitosis of these cells is unimportant; the whole process of osteo-arthritis evolves exceedingly slowly; it is spread over years of time and is therefore not to be compared with such processes as the growth of granulation tissue or neoplasia in which the pathologist is accustomed to see mitoses; adult cartilage, unlike epidermis or intestinal mucosa, is a highly stable tissue, virtually incapable even of self-repair. Indeed, our present histological studies give no indication that the active chondrocytes of disintegrating osteo-arthritic cartilage are capable of any other function than the elaboration of sulphated mucopolysaccharides; they do not seem to regenerate the collagen fibres of the cartilage, nor do they revert to a fibroblastic or undifferentiated form of mesenchymal cell.

The cell clumps in fibrillated cartilage have been known for 40 years or more; their significance was never clear, because no one knew just what these cells were doing. Now it has been demonstrated that they are attempting to make good the loss of mucopolysaccharide matrix. Our findings seem finally to refute the view that the initial cartilage lesion is a cellular necrosis, and they support the more widely-held view (see Bennett, Waine, and Bauer, 1942, for discussion) that the earliest disturbance is one of the intercellular substance. Silberberg, Frank, Jarrett, and Silberberg (1959) noted certain changes in the histochemical reactions of cartilage matrix in human sternoclavicular joints indicating biochemical and biophysical changes, which they believed might interfere with the restraining influence usually exerted by the matrix on cell growth and might thereby release the dormant growth potential of the cartilage cells. This, on general principles, is an acceptable idea. The results of the stimulated chondrocyte growth and activity, however, fall short of an effective repair of the cartilage's defects, though, perhaps, the new production of sulphated acid mucopolysaccharides may for long delay its final disintegration.

The staining reactions which we have observed in articular cartilage are in line with those recorded by Fawns and Landells (1953). Particular points on which we agree are the general reciprocity of P.A.S. and metachromatic staining, the feeble staining of any mucopolysaccharides in Zone 1, the metachromatic pools around the cells in Zones 2 and 3, the absence of metachromasia in deep Zone 3 in older subjects, and the great intensity of P.A.S. staining in haloes around the cells of the calcified Zone 4.

Some additional points emerge from our studies: first, confirmation of the fact that alcian blue stains strongly in areas that also show metachromasia; secondly, the association of metachromasia and alcian-blue staining with active synthesis of chondroitin sulphate, as shown in the autoradiographs, and the negative P.A.S. reaction around cells that are fixing sulphate. The cells in the calcified zone of articular cartilage that are surrounded by a P.A.S.-positive halo seem to have little or no power of utilizing sulphate.

It is now generally agreed that alcian-blue staining and metachromasia both indicate the presence of acid mucopolysaccharides, commonly, but not necessarily, sulphated. A positive reaction with P.A.S. is much less specific, since P.A.S.-positive substances are of many kinds and include polysaccharides like glycogen, neutral mucopolysaccharides, mucoproteins and glycoproteins, glycolipids and some other unsaturated lipids, and phospholipids (Pearse, 1960). Some of the P.A.S. staining in cartilage may be more closely associated with its collagen fibrils than with its diffuse matrix. Basophilia with an acid haematoxylin corresponds mainly with metachromasia and likewise indicates the probable presence of acid mucopolysaccharides so far as haematoxylin staining of intercellular material is concerned.

When we consider all that may be observed in the various histological preparations we have used, we are bound to conclude that at every stage of osteo-arthritis it is loss of mucopolysaccharide matrix (chondroitin sulphate) that constitutes the primary lesion in the cartilage.

At the earliest stage, the superficial cartilage matrix changes its staining properties and seems to shrink and to crack along the tangentially disposed fibre lines (Fig. 6). Fibrillation then extends into the oblique-fibred Zone 2 (Figs 10 and 11) and then vertically through Zone 3 (Figs 15, 17, and 18). Metachromasia, basophilia, and alcian-blue staining are lost from this disintegrating matrix, but the fibres survive (Fig. 23) and the P.A.S. reaction is sometimes maintained in the region of these fibres. Finally, all the uncalcified cartilage of Zones 1 to 3 is sheared off at the level of the calcified Zone (Fig. 16), and ultimately such an area may be worn down to a polished eburnated surface of hyperplastic bone with no cartilaginous residues.

The reaction of the chondrocytes to this loss of matrix is vigorous in all areas of uncalcified cartilage except the most superficial. Proliferation of cartilage cells is accompanied by enhancement of chondroitin sulphate synthesis, but, because this seems to be the only capacity they retain, the cellular reaction is incapable of permanently preventing the ultimate disintegration of the cartilage or of repairing it in any structurally effective way.

Summary

The uptake of labelled sulphate ($^{35}SO_4$) *in vitro* by normal and osteo-arthritic human articular cartilage has been measured and studied in autoradiographs. The findings have been considered in conjunction with observations on histological sections of the same cartilages stained for cells and for the mucopolysaccharide and fibrillar components of matrix.

Increasing avidity for sulphate is displayed by cartilage that shows increasing grades of osteo-arthritis. This is a cellular function and represents a stimulation of cells to manufacture chondroitin sulphate in response to loss of the matrix that surrounds them.

The cells most active in this respect are those that have proliferated to form large clusters lying between the fissures of fibrillated cartilage in the middle Zones (2 and 3); cells of the superficial zone (Zone 1) are effete, and they and the cells incarcerated in the calcified zone of cartilage (Zone 4) do not respond to any extent either by proliferation or by enhanced sulphate utilization.

Metachromasia and alcian-blue staining are found where sulphated acid mucopolysaccharides are being formed. These reactions tend to be lost as cartilage disintegrates.

The periodic acid-Schiff reaction (P.A.S.) of articular cartilage is difficult to interpret: it is usually absent where metachromasia is strong and *vice versa*; it seems often to be associated with the collagen fibril bands in cartilage and, with the fibres, may still be observed in disintegrating cartilage after the metachromatically staining material has been dispersed.

All our observations lead to the conclusion that the original lesion of cartilage in osteo-arthritis is a dissolution of the acid mucopolysaccharide fraction of its matrix.

The work here reported was performed with the aid of a research grant from the Empire Rheumatism Council for which we are very grateful.

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Absorption de sulfate ($^{35}SO_4$) par les chondrocytes en relation aux altérations histologiques dans le cartilage articulaire humain ostéoarthritique

Résumé

On a mesuré et étudié à l'autoradiographie *in vitro* l'absorption de sulfate marqué ($^{35}SO_4$) par le cartilage articulaire humain, normal et ostéoarthritique. On a considéré les résultats en relation aux observations des coupes histologiques des mêmes cartilages, colorées pour mettre en évidence les cellules et les composants mucopolysaccharides et fibrillaires de la matrice.

L'absorption de sulfate par le cartilage augmente au fur et à mesure que l'ostéoarthrite s'empire. C'est une fonction cellulaire et représente une stimulation des cellules à produire du sulfate de chondroitine en réponse à la perte de la substance de base.

Les cellules le plus actives de ce point de vue sont celles qui ont proliféré de grands amas situés entre les fissures du cartilage fibrillaire dans les zones moyennes (2 et 3); les cellules de la zone superficielle (zone 1) sont épuisées et, comme les cellules incarcérées dans la zone calcifiée du cartilage (zone 4), ne répondent guère par la prolifération ni par l'utilisation augmentée de sulfate.

On trouve de la métachromasie et de la coloration au bleu d'alcian là où se forment des mucopolysaccharides acides sulfatés. Ces réactions tendent à disparaître à mesure que le cartilage se décompose.

La réaction acide-Schiff périodique (P.A.S.) du cartilage articulaire est difficile à interpréter: elle est généralement absente quand la métachromasie est prononcée et vice versa; souvent elle semble être associée aux bandes fibrillaires de collagène dans le cartilage et on peut encore l'observer, avec les fibres, dans le cartilage en désintégration, après que le matériel coloré métachromatiquement ait été dispersé.

Toutes nos observations mènent à la conclusion, que la lésion originale du cartilage dans l'ostéoarthrite est la dissolution de la fraction mucopolysaccharide acide dans la matrice.

Absorción de sulfato ($^{35}SO_4$) por los condrocitos en relación con los cambios histológicos en el cartilago articular humano osteoartritico

Sumario

La absorción de sulfato marcado ($^{35}SO_4$) por cartílago articular humano, normal y osteoartrítico, ha sido estudiado *in vitro* por mediciones y autorradiografía. Los hallazgos se han considerado en relación con observaciones de secciones histológicas de los mismos cartílagos teñidas para visualizar las células así como los componentes mucopolisacarido y fibrilar de la substancia de base.

Progresiva avidez por el sulfato se manifesta en el cartílago que presenta grados progresivos de osteoartritis. Se trata aqui de una función celular, representando una estimulación de las células a la producción de sulfato de condroitina como respuesta a la perdida de la substancia básica que la rodea.

Las células más activas a este respecto son aquellas que han proliferado procedentes de grandes grupos situados entre las fisuras del cartílago fibrilado en las zonas medias (2 y 3); las células de la zona superficial (zona 1) están agotadas y ellas, así como las células englosadas en la zona de cartílago calcificado (zona 4) no responden en absoluto ni por proliferación ni por utilización mayor de sulfato.

Metacromasia y tinción con azul-alcian aparecen donde mucopolisacaridos ácidos sulfatados están en formación. Estas reacciones tienden a desaparecer a medida que el cartílago se desintegra.

La reacción ácido-Schiff periódica (P.A.S.) del cartílago articular es difícil de interpretar: está usualmente ausente cuando la metacromasia es pronunciada y viceversa; a menudo parece estar asociada con fajas fibrilares de colágeno en el cartílago y puede aún ser observada con las fibras en cartílago en desintegración después que el material teñido metacromáticamente ha sido dispersado.

Todas nuestras observaciones conducen a la conclusión de que la lesión original del cartílago en la osteoartritis es una disolución de la fracción mucopolisacarida ácida de su substancia base.

Ann. rheum. Dis. (1960), **19**, 331.

A COMPARISON OF PREDNISOLONE WITH ASPIRIN OR OTHER ANALGESICS IN THE TREATMENT OF RHEUMATOID ARTHRITIS

A SECOND REPORT BY THE JOINT COMMITTEE OF THE MEDICAL RESEARCH COUNCIL AND NUFFIELD FOUNDATION ON CLINICAL TRIALS OF CORTISONE, ACTH, AND OTHER THERAPEUTIC MEASURES IN CHRONIC RHEUMATIC DISEASES*

In 1955 the Joint Committee initiated a controlled therapeutic trial designed to compare the value of prednisolone with that of aspirin or other analgesics in the treatment of defined cases of rheumatoid arthritis. Eight centres participated and 84 patients entered the trial, a detailed description of which was published in a previous report (1959). During the first 2 years of treatment the patients receiving prednisolone showed an early significant improvement in both clinical and laboratory indices of inflammatory polyarthritis, and less progression of radiological signs of erosive joint disease, but in many patients treated with prednisolone a rise in agglutinating titre in the sheep cell agglutination test was noted and five patients had major complications (two psychoses, three peptic ulcers). In this report we are concerned only with the changes which occurred during the third year of treatment in the 76 patients who remained in the trial at the end of its second year.

Towards the end of the third year one male patient in the prednisolone group died from carcinoma of the colon. His arthritis remitted at the end of the second year and he developed psoriasis of skin and nails, but he was fully assessed 2½ years after entry into the trial and these assessments have been included in the analysis of the third year's results. All the remaining 75 patients were reassessed at approximately 3 years from the date of their entry into the trial.

Of the total 76 patients, 41 were originally allocated to prednisolone and 35 to analgesics, but towards the end of the second year the treatment was changed in a number of patients, so that during the third year nine of the 35 patients in the analgesics group were receiving prednisolone in addition to analgesics, and seven of the 41 patients in the prednisolone group were no longer receiving this drug. During the third year one of these seven patients was being treated with dexamethazone, one with corticotrophin, one with aspirin, and four (including the man who died) were recorded as taking no tablets of any kind. Many of the patients treated with prednisolone, however, also took a varying number of analgesic tablets of which the main constituent was aspirin.

Since the results of the first 2 years showed a significant difference between patients treated with prednisolone and those being treated with analgesics, the nine patients who received prednisolone in addition to analgesics during the third year have been analysed separately from the 26 patients who continued on analgesics throughout the 3 years. The mean daily dose of prednisolone at the end of

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PARTICIPATING PHYSICIANS: Prof. E. G. L. Bywaters (Postgraduate Medical School of London), Dr. W. S. C. Copeman and Dr. O. Savage (West London Hospital Medical School), Dr. J. J. R. Duthie (Rheumatic Unit, Northern General Hospital, Edinburgh), Dr. A. G. S. Hill (Oxford Regional Rheumatic Diseases Research Centre), Prof. J. H. Kellgren (Rheumatism Research Centre, Manchester), Dr. G. D. Kersley (Royal National Hospital for Rheumatic Diseases, Bath), Dr. R. M. Mason (Department of Physical Medicine and Regional Rheumatism Centre, London Hospital), Dr. H. F. West (Sheffield Centre for the Investigation and Treatment of Rheumatic Diseases).

STATISTICAL ANALYSIS: Dr. W. J. Martin (M.R.C. Statistical Research Unit, London School of Hygiene and Tropical Medicine).

the second year was 10 mg., and at the end of the third year it was 10·5 mg.; there was little change in dosage during the third year.

Results

The general condition of the patients in the two treatment groups (as judged by the physician's opinion about disease activity, functional capacity, joint pain and tenderness, and joint swelling) are shown in Tables I to IV, in which the findings on entry into the trial and after 2 and 3 years of treatment are shown. At the start the prednisolone group contained rather more severely disabled patients with a high grade of disease activity than the analgesics group, but at the third year assessment this difference was reversed, the prednisolone group containing more patients judged to have no disease activity or a normal (Grade 1) functional status. The records of joint pain and swelling, however, showed only minor differences.

The changes in the strength of grip and body

TABLE I

NUMBER OF PATIENTS WITH GIVEN GRADE* OF DISEASE ACTIVITY

Time of Assessment	Treatment Group	Grade				Total
		0	1	2	3	
Week 0	Analgesics throughout trial	—	9	16	1	26
	Changed to prednisolone in 2nd or 3rd year	—	4	4	1	9
	All analgesics patients	—	13	20	2	35
	Prednisolone	—	9	27	5	41
Year 2	Analgesics throughout trial	4	15	7	—	26
	Changed to prednisolone in 2nd or 3rd year	—	7	2	—	9
	All analgesics patients	4	22	9	—	35
	Prednisolone	5	30	6	—	41
Year 3	Analgesics throughout trial	3	17	6	—	26
	Changed to prednisolone in 2nd or 3rd year	—	6	3	—	9
	All analgesics patients	3	23	9	—	35
	Prednisolone	10	20	9	2	41

* Grade: 0 = None 1 = Slight 2 = Moderate 3 = Severe.

TABLE II

NUMBER OF PATIENTS WITH GIVEN GRADE* OF FUNCTIONAL CAPACITY

Time of Assessment	Treatment Group	Grade					Total
		1	2	3	4	5	
Week 0	Analgesics throughout trial	—	5	19	2	—	26
	Changed to prednisolone in 2nd or 3rd year	—	2	5	1	1	9
	All analgesics patients	—	7	24	3	1	35
	Prednisolone	—	11	16	9	5	41
Year 2	Analgesics throughout trial	8	14	3	—	1	26
	Changed to prednisolone in 2nd or 3rd year	1	4	4	—	—	9
	All analgesics patients	9	18	7	—	1	35
	Prednisolone	19	18	3	1	—	41
Year 3	Analgesics throughout trial	9	15	2	—	—	26
	Changed to prednisolone in 2nd or 3rd year	1	6	1	1	—	9
	All analgesics patients	10	21	3	1	—	35
	Prednisolone	23	13	3	2	—	41

* Grade: 1 = Fully employed or employable in normal work and able to undertake normal physical recreations for their type.
2 = Fully employed in special work after vocational training, or doing light or part-time work in normal occupation. Limitation in the amount of physical recreation. Housewives, all except the heaviest housework. In-patients, in hospital for investigation only.
3 = Not employed or employable. Very limited physical activity and little or no capacity for physical recreation. Housewives, light housework and/or limited shopping only. In-patients in hospital for treatment, but up and about in ward.
4 = Confined to hospital, house, or wheelchair, but able to look after themselves in the essentials of life. In-patients in hospital for treatment, sitting up but not getting about.
5 = Confined to bed and unable to look after themselves. In-patients on complete rest in bed.

TABLE III

NUMBER OF PATIENTS WITH GIVEN GRADE* OF JOINT PAIN OR TENDERNESS

Time of Assessment	Treatment Group	Grade				Total
		0	1	2	3	
Week 0	Analgesics throughout trial	—	8	14	4	26
	Changed to prednisolone in 2nd or 3rd year	—	3	6	—	9
	All analgesics patients	—	11	20	4	35
	Prednisolone	—	13	19	9	41
Year 2	Analgesics throughout trial	3	17	6	—	26
	Changed to prednisolone in 2nd or 3rd year	—	6	2	1	9
	All analgesics patients	3	23	8	1	35
	Prednisolone	9	22	10	—	114
Year 3	Analgesics throughout trial	5	16	5	—	26
	Changed to prednisolone in 2nd or 3rd year	2	6	1	—	9
	All analgesics patients	7	22	6	—	35
	Prednisolone	13	17	8	3	41

* Grade: 0 = None 1 = Slight 2 = Moderate 3 = Severe.

TABLE IV

NUMBER OF PATIENTS WITH GIVEN GRADE* OF JOINT SWELLING

Time of Assessment	Treatment Group	Grade				Total
		0	1	2	3	
Week 0	Analgesics throughout trial	1	11	13	1	26
	Changed to prednisolone in 2nd or 3rd year	—	3	6	—	9
	All analgesics patients	1	14	19	1	35
	Prednisolone	1	20	18	2	41
Year 2	Analgesics throughout trial	5	13	8	—	26
	Changed to prednisolone in 2nd or 3rd year	—	5	4	—	9
	All analgesics patients	5	18	12	—	35
	Prednisolone	16	18	7	—	41
Year 3	Analgesics throughout trial	6	15	4	1	26
	Changed to prednisolone in 2nd or 3rd year	1	7	1	—	9
	All analgesics patients	7	22	5	1	35
	Prednisolone	14	20	7	—	41

* Grade: 0 = None 1 = Slight 2 = Moderate 3 = Severe.

weight, and the results of laboratory tests such as the erythrocyte sedimentation rate, haemoglobin concentration, and white cell count, are shown in Table V (overleaf).

The strength of grip in the prednisolone group showed a slight fall during the third year, but the difference between the initial and third-year grip for both hands remained significant ($p < 0{\cdot}01$), whereas the improvement in grip in the analgesics group failed to reach conventional levels of significance.

The erythrocyte sedimentation rate (recorded by the Westergren technique) showed a rise of 2 mm./hr in the mean of the prednisolone group and a fall of 1 mm./hr in the group of 26 patients who received analgesics throughout the trial. At both the 2nd and 3rd year assessments the average erythrocyte sedimentation rate for both treatment groups was almost the same and still below the level at the start of the trial.

The haemoglobin concentration showed little change during the third year, the mean value in the prednisolone group being still slightly higher than that of the analgesics group at the end of the third year. The mean white cell counts showed no significant change.

The mean body weight of the patients who received analgesics throughout the trial increased by 2 lb. during the third year, whereas the patients in the prednisolone group showed a fall of ½ lb. Since

TABLE V

AVERAGE MEASUREMENTS OF VARIOUS CHARACTERISTICS

Time of Assessment	Treatment Group	Strength of Grip (mm. Hg)		Erythrocyte Sedimentation Rate (mm./1 hr, Westergren)	Hb (g. per cent.)	White Cell Count	Body Weight (lb.)
		Left hand	Right hand				
Week 0	Analgesics throughout trial	148	142	33	13·3	8,900	135·2
	Changed to prednisolone in 2nd or 3rd year	93	99	45	12·6	9,200	137·2
	All analgesics patients	133	131	36	13·1	8,900	135·7
	Prednisolone	119	110	41	12·7	8,300	141·4
Year 2	Analgesics throughout trial	162	178	27	13·3	8,000	136·0
	Changed to prednisolone in 2nd or 3rd year	123	119	35	12·7	10,000	143·3
	All analgesics patients	152	163	29	13·2	8,500	137·7
	Prednisolone	195	199	25	13·7	9,500	145·8
Year 3	Analgesics throughout trial	160	183	26	13·3	8,100	138·6
	Changed to prednisolone in 2nd or 3rd year	120	117	23	12·9	9,100	142·2
	All analgesics patients	150	166	25	13·2	8,400	139·5
	Prednisolone	191	195	27	13·6	8,900	145·3

the prednisolone group had shown a greater rise in body weight earlier in the trial when a higher dosage was given, the findings at the third-year assessment are the same, the mean body weight in both treatment groups at 3 years being 4 lb. greater than it was initially.

The results shown in Tables I to V demonstrate a small but definite advantage to prednisolone therapy compared with treatment with aspirin or other analgesics, and this advantage was still present at the end of the third year of treatment. The records of the nine patients who were originally allocated to analgesics and later changed to prednisolone suggest that these patients had a more serious disease and did less well than the average patient in the analgesics group, so that if these nine patients had continued on analgesics only throughout the trial the difference between the original treatment groups at the third year assessment might have been more pronounced.

X-Ray Changes

The *x* rays of the hands and feet taken at 2 and 3 years after entry into the trial were read by one observer (J.H.K.) who was unaware of the treatment given. As in the previous report, each film was given a grading for rheumatoid changes (0 = None, 1 = Doubtful, 2 = Definite but Slight, 3 = Moderate, 4 = Severe). In computing these grades, changes such as articular erosion, joint narrowing or subluxation, and osteoporosis were all taken into account. In addition, an opinion was expressed about improvement, deterioration, or no change between the second and third-year films, since such changes were not always of sufficient magnitude to alter the rather coarse grading employed.

The number of patients showing changes in grade between the second and third year films* are shown in Table VI, and the numbers showing improvement or deterioration in Table VII. Slight radiological improvement was noted in only a few patients, whereas over one-third of the patients in both treatment groups show some radiological deterioration; this was perhaps slightly greater in the prednisolone group, but the overall picture is one of little change during the third year.

Table VIII shows the actual gradings of rheumatoid change seen in the films of hands and feet taken at the start of the trial and after 2 and 3 years of treatment. There was much more progression of radiologically demonstrable joint change amongst the patients allocated to analgesics than amongst those allocated to prednisolone, although both groups were comparable at the start. In the analgesics group the differences between the rheumatoid gradings of the initial and the 3-year films of the hands and feet show $p < 0{\cdot}0001$ and $p < 0{\cdot}02$ respectively. These differences are even greater than those between the initial and the 2-year films previously reported. In the prednisolone group p has now reached $< 0{\cdot}05$ for the differences in grading between the initial and the 3-year films of the hands, but remains not formally significant with regard to the feet films.

* Films of one patient in the analgesic group who was Grade 4 at 2 years were not available at 3 years.

TABLE VI

CHANGES IN RHEUMATOID GRADING OF *X*-RAY FILMS OF HANDS AND FEET DURING THE 3RD YEAR

Films	Treatment Group	Change in Grade (3-yr minus 2-yr)					Total
		+2	+1	0	−1	−2	
Hands	Analgesics throughout trial	—	5	21	—	—	26
	Changed to prednisolone in 2nd or 3rd year	—	—	8	—	—	8
	All analgesics patients	—	5	29	—	—	34
	Prednisolone	—	4	36	1	—	41
Feet	Analgesics throughout trial	—	1	24	1	—	26
	Changed to prednisolone in 2nd or 3rd year	—	1	7	—	—	8
	All analgesics patients	—	2	31	1	—	34
	Prednisolone	1	3	36	1	—	41

TABLE VII

IMPROVEMENT OR DETERIORATION IN *X*-RAY FILMS OF HANDS AND FEET DURING THE 3RD YEAR

Films	Treatment Group	3-year Compared with 2-year Films			Total
		Deterioration	No Change	Improvement	
Hands	Analgesics throughout trial	13	12	1	26
	Changed to prednisolone in 2nd or 3rd year	2	6	—	8
	All analgesics patients	15	18	1	34
	Prednisolone	16	24	1	41
Feet	Analgesics throughout trial	4	20	2	26
	Changed to prednisolone in 2nd or 3rd year	1	6	1	8
	All analgesics patients	5	26	3	34
	Prednisolone	11	29	1	41

TABLE VIII

ACTUAL GRADING OF RADIOLOGICAL CHANGES OF RHEUMATOID ARTHRITIS IN FILMS OF HANDS AND FEET AT VARIOUS PERIODS

Films	Time of Assessment	Treatment Group	Grade					Total
			0	1	2	3	4	
Hands	Initial	Analgesics	13	5	11	5	1	35
		Prednisolone	15	8	13	4	1	41
	Year 2	Analgesics	3	2	13	11	6	35
		Prednisolone	9	8	16	4	4	41
	Year 3	Analgesics	3	2	8	16	5	34
		Prednisolone	9	7	14	7	4	41
Feet	Initial	Analgesics	10	6	9	8	1	34
		Prednisolone	10	7	14	9	1	41
	Year 2	Analgesics	5	2	10	14	4	35
		Prednisolone	12	3	14	9	3	41
	Year 3	Analgesics	4	3	11	12	4	34
		Prednisolone	11	3	13	11	3	41

Grade: 0 = None 1 = Doubtful 2 = Slight 3 = Moderate 4 = Severe.

Sheep Cell Agglutination Test

Details of the techniques used by the participating centres were given in the previous report. Since these were not uniform the minimal positive titre used by each centre has been taken as zero, and dilutions above and below this have been scored as +1, +2, etc., and −1, −2, etc.; the results* so

* Agglutination test results of the patient in the prednisolone group who died (negative at 2 years), and of one patient in the analgesics group (low positive at 2 years) were not available at the 3-year assessment.

obtained are set out in Table IX. The distribution of agglutinating titres within the two treatment groups was very similar at the start of the trial. After 2 years' treatment there were more patients in the prednisolone group with high titres, whereas the distribution of titres in the analgesics group remained unchanged. This tendency for the titre to rise in the prednisolone group did not continue in the third year and indeed there were slightly fewer patients with high titres in the prednisolone group at the 3-year assessment than there had been at the 2-year assessment.

Complications

During the third year of the trial no major complications were reported and the records of minor complications (Table X) show that moon face, hirsuties, euphoria, and depression were still noted in some patients receiving prednisolone in spite of the lower mean dosage employed during the second and third years of the trial. The barium meals and spinal *x* rays which were done at the 2-year assessment were not repeated at the 3-year assessment.

TABLE IX

RESULTS OF SHEEP CELL AGGLUTINATION TESTS*

Time of Assessment	Treatment Group	Results of Tests							Total Positive and Negative
		Negative			Positive				
		−5 to −3	−2 to −1	Total	0 to +1	+2 to +3	+4 to +7	Total	
Initial	Analgesics throughout trial	4	4	8	7	8	3	18	26
	Changed to prednisolone in 2nd or 3rd year	2	2	4	1	2	2	5	9
	All analgesics patients	6	6	12	8	10	5	23	35
	Prednisolone	5	8	13	14	11	3	28	41
Year 2	Analgesics throughout trial	3	8	11	7	5	3	15	26
	Changed to prednisolone in 2nd or 3rd year	2	1	3	2	2	2	6	9
	All analgesics patients	5	9	14	9	7	5	21	35
	Prednisolone	6	6	12	5	12	12	29	41
Year 3	Analgesics throughout trial	3	8	11	7	3	5	15	26
	Changed to prednisolone in 2nd or 3rd year	2	1	3	1	2	2	5	8
	All analgesics patients	5	9	14	8	5	7	20	34
	Prednisolone	3	11	14	8	9	9	26	40

* Based on minimal positive titre = 0, with deviations above and below in numbers of tubes showing agglutination.

TABLE X

NUMBER OF PATIENTS WITH GIVEN SIDE-EFFECTS

Time of Assessment	Treatment Group	Tinnitus or Deafness	Dyspepsia	Moonface	Acne	Hirsuties	Oedema	Euphoria	Depression
Week 0	Analgesics throughout trial	—	1	—	—	1	—	—	2
	Changed to prednisolone in 2nd or 3rd year	1	1	—	—	—	1	—	2
	All analgesics patients	1	2	—	—	1	1	—	4
	Prednisolone	2	3	—	—	—	2	1	4
Year 2	Analgesics throughout trial	1	4	—	—	—	2	—	—
	Changed to prednisolone in 2nd or 3rd year	—	3	4	—	1	—	—	—
	All analgesics patients	1	7	4	—	1	2	—	—
	Prednisolone	2	8	14	3	2	2	3	2
Year 3	Analgesics throughout trial	1	3	—	—	—	—	—	—
	Changed to prednisolone in 2nd or 3rd year	—	2	4	—	—	—	—	—
	All analgesics patients	1	5	4	—	—	—	—	—
	Prednisolone	—	5	15	—	2	—	1	4

Discussion

During the third year of observation there was remarkably little change. Many patients in both treatment groups deteriorated slightly and a few improved a little. The difference between the two treatment groups previously noted was still significant at the end of 3 years, though it was less than it had been earlier. The results are, however, complicated by the fact that nine of the patients in the analgesics group who were not doing well at the end of the second year received prednisolone during the third year.

During the first 2 years of the trial the sheep cell agglutinating titre rose to high levels in many patients treated with prednisolone, but this tendency to rising titres did not continue and at the 3-year assessment there were in fact fewer patients with very high titres than had been at the end of the second year. The suppression of articular erosion obtained with prednisolone during the earlier part of the trial when a higher dosage was given was less evident during the third year, during which the mean dosage was between 10 and 10·5 mg. daily, since at this lower dosage there was roughly equal deterioration of the radiological appearances in the films of hands and feet in both treatment groups, and it may be that the striking advantage to prednisolone as compared with analgesics described in the first report of this trial was largely due to the profound suppressive effects of the higher dosage used in the first year, which unfortunately proved to be unacceptable because of serious side-effects such as psychosis and bleeding peptic ulceration. Alternatively, the effectiveness of prednisolone in suppressing erosions may diminish after years of administration. The long-term complications of corticosteroid therapy (such as osteoporosis, thinning of the skin and blood vessels, senile purpura, etc.) may still develop, so that many more years of observation will be required before the true long-term balance sheet comparing the advantages and disadvantages of corticosteroid therapy can be drawn up.

Summary

In 1955 a controlled trial comparing prednisolone with analgesics in the treatment of certain defined cases of rheumatoid arthritis was initiated, and the results of the first 2 years of the trial have already been reported.

During the third year many of the patients in both treatment groups deteriorated slightly and one or two improved, but the overall picture was one of little change. The advantage to prednisolone demonstrated at the 2-year assessment was still present to a significant but slightly lower degree at the 3-year assessment.

The tendency for the sheep cell agglutinating titre to rise during the first 2 years in some patients treated with prednisolone did not continue during the third year.

REFERENCE

Joint Committee of the Medical Research Council and Nuffield Foundation on Clinical Trials of Cortisone, ACTH and Other Therapeutic Measures in Chronic Rheumatic Diseases (1959). *Ann. rheum. Dis.*, **18**, 173.

Comparaison de la prednisolone avec l'aspirine ou d'autres analgésiques dans le traitement de l'arthrite rheumatismale

RÉSUMÉ

En 1955 on a entrepris un essai contrôlé, comparant la prednisolone avec d'autres analgésiques dans le traitement de certains cas définis d'arthrite rhumatismale et on a déjà publié les résultats des premiers deux ans de cet essai.

Pendant la troisième année on a noté une légère détérioration chez beaucoup de malades des deux groupes de traitement et une amélioration chez un ou deux d'entre eux, mais le tableau général était peu changé. L'avantage de la prednisolone, démontré à l'évaluation des résultats de deux ans, demeurait appréciable mais un peu inferieur à l'évaluation de la troisième année.

La tendance à monter du titre d'agglutination des globules sensibilisés de mouton chez certains malades traités par la prednisolone pendant les premiers deux ans n'a pas continué pendant la troisième année.

Comparación de la prednisolona con la aspirina u otros analgésicos en el tratamiento de la artritir reumatoide

SUMARIO

En 1955 se inició una prueba controlada comparando la prednisolona con los analgésicos en el tratamiento de ciertos definidos casos de artritis reumatoide, y los resultados de los dos promeros años de la prueba han sido ya publicados.

Durante el tercer año muchos de los enfermos de ambos grupos de tratamiento empeoraron ligeramente y uno o dos mejoraron, pero el cuadro predominante fué de escasa variación. La ventaja de la prednisolona, demostrada en las investigaciones de dos años estaba presente todavía de una forma significativa, pero en un grado ligeramente inferior, en las comprobaciones del tercer año.

La tendencia a la elevación del título de aglutinación de los eritrocitos sensibilizados de carnero en algunos pacientes tratados con prednisolona durante los dos primeros años, no continuó durante el tercer año.

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INCIDENCE OF THE ANTI-NUCLEAR FACTOR IN HUMAN SERA

BY

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Miescher and Fauconnet (1954) reported that the ability of serum from patients suffering from disseminated lupus erythematosus (D.L.E.) to induce the formation of L.E. cells was abolished if the serum was previously incubated with nuclear material. Friou (1957), using the Coons' technique, showed that cells in unfixed sections of tissue exposed to serum from patients with D.L.E. and, subsequently, to fluorescein-conjugated anti-human globulin serum, exhibited nuclear fluorescence. The presence of an anti-nuclear factor (A.N.F.) in this disease has been confirmed by other workers and the subject has recently been reviewed by Holman and Kunkel (1959).

Goodman, Fahey, Malmgren, and Brecher (1959) have identified A.N.F. as a gamma globulin, separable from that associated with the formation of L.E. cells. The presence of identical or closely-related globulins has now been reported in other diseases, particularly in those characterized by involvement of connective tissues. The results of several investigations are summarized in Table I.

Using the Coons' fluorescent antibody technique, A.N.F. was detected in sixty of the 62 cases of D.L.E. tested (97 per cent.) and was also present in a proportion of cases of scleroderma, dermato-myositis and polyarteritis nodosa. The incidence of A.N.F. in rheumatoid arthritis has been variously reported as less than 10 per cent. by Friou (1958a), 16 per cent. by Holborow and Weir (1958), and 48 per cent. by Duthie, Bremner, and Alexander (1959). The series of Bardawil, Toy, Galins, and Bayles (1958) is too small to be significant, but Bardawil, Hall, and Bayles (in a communication to the American Rheumatism Association quoted by Sokoloff, Bloch, Seegmiller, Stollerman, and Yielding, 1959) detected A.N.F. in 39 per cent. of cases of severe rheumatoid arthritis. Fessel (1959), using latex particles coated with nucleoprotein as an indicator, demonstrated A.N.F. in 23 per cent. of 150 rheumatoid sera tested.

Few positive results have been obtained in diseases other than those affecting connective tissue, and the observation by Friou (1958a) and Fessel (1959) that A.N.F. was present in a number of sera exhibiting false positive reactions for syphilis is interesting in view of the speculations of Moore (1956) on the possible relationship of biologic false positive reactions to diseases of connective tissue. Weir (1959) reported the presence of A.N.F. in five of 38 sera from patients suffering from hepatic disease and in 10 per cent. of patients with disease of the thyroid gland.

A.N.F. has been demonstrated in most cases of D.L.E., but the reported incidence in rheumatoid arthritis has varied widely (Table I, opposite).

This suggests that the techniques used in the several investigations differed in sensitivity, but that A.N.F. was always present in sufficiently large amounts in D.L.E. to be detected even by the less sensitive techniques. Friou (1958b), using a semi-quantitative method, has already shown that A.N.F. is usually present in higher titre in D.L.E. than in rheumatoid arthritis.

It seemed important, in view of these results and the current view that A.N.F. may be of pathogenic significance in D.L.E., to screen a large number of human sera for A.N.F. by a sensitive technique.

The results of a survey of 1,116 sera are presented in this report with special reference to the prevalence and possible significance of A.N.F. in rheumatoid arthritis.

TABLE I

SUMMARY OF PREVIOUS INVESTIGATIONS

Authors		Friou		Holborow and Weir		Bardawil, Toy, Galins, and Bayles		Duthie, Bremner, and Alexander		Fessel	
Date		(1958a)		(1958)		(1958)		(1959)		(1959)	
Technique		Coons' fluorescent antibody (indirect)								Latex agglutination	
Substrate		Calf thymus nucleo-histone		Sections of frozen tissue				Human blood film		Latex particles coated with nucleoprotein	
Number of Cases		Tested	Positive	Tested	Positive	Tested	Positive	Tested	Positive	Tested	Positive
Diagnosis	Disseminated lupus erythematosus	35	35	12	10	5	5	10	10	37	25
	Scleroderma	3	1	—	—	10	9	1	1	—	—
	Dermatomyositis	2	1	1	0	2	1	—	—	—	—
	Polyarteritis nodosa	—	—	2	0	—	—	1	1	—	—
	Rheumatoid arthritis	42	4 (10%)	49	8 (16%)	8	5	264	127 (48%)	150	35 (23%)
	Juvenile rheumatoid arthritis	—	—	15	3	—	—	1	0	—	—
	Rheumatic fever	13	0	18	0	—	—	3	0	—	—
	Ankylosing spondylitis	—	—	1	0	—	—	4	0	—	—
	Other rheumatic diseases	—	—	—	—	—	—	19	0	—	—
	Chronic biologic false positive reactors	17	4	—	—	—	—	—	—	18	7
	Other	257	4* (<2%)	—	—	17	0	29	1†	—	—

* Neoplasm with metastases 1; Syphilis 2; Drug reaction 1 } 4

† Reticulosis 1

Material and Methods

Sera from 511 males and 605 females were titrated for A.N.F. Table II shows the sex and age groups of these individuals and the diagnostic categories to which they were assigned.

The small group of nineteen patients (Table III, overleaf) suffering from the classical "collagen diseases" was composed of twelve cases of D.L.E., in all of whom the L.E. cell test was positive, three cases each of scleroderma and polyarteritis nodosa, and one case of dermatomyositis. The L.E. cell test was negative in these patients.

The 183 patients suffering from rheumatoid arthritis were members of a group who had attended the rheumatic clinic for a number of years and had been studied in detail by Duthie, Thompson, Weir, and Fletcher (1955), Duthie, Brown, Knox, and Thompson (1957), and Brown

TABLE II

COMPOSITION OF GROUPS BY AGE AND SEX

Sex	Group	Age (yrs)						Total
		−24	−34	−44	−54	−64	65+	
Male	Disseminated lupus erythematosus, polyarteritis nodosa, dermatomyositis, scleroderma	—	—	1	1	—	1	3
	Rheumatoid arthritis	—	3	5	10	18	9	45
	Generalized osteo-arthritis, osteo-arthrosis, disk degeneration, other rheumatic diseases	9	9	3	19	8	12	60
	Miscellaneous diseases	7	9	6	12	9	12	55
	Controls	64	107	85	67	22	3	348
	Total							511
Female	Disseminated lupus erythematosus, polyarteritis nodosa, dermatomyositis, scleroderma	4	5	2	1	2	2	16
	Rheumatoid arthritis	—	2	14	35	52	35	138
	Generalized osteo-arthritis, osteo-arthrosis, disk degeneration, other rheumatic diseases	8	4	8	25	36	24	105
	Miscellaneous diseases	5	23	20	28	17	21	114
	Controls	60	50	64	47	9	2	232
	Total							605
Total Both Sexes								1,116

and Duthie (1958). The serological, haematological, and clinical data included in the present report were obtained at an assessment of the patients in 1959. At this time the mean age of the group was 57 years and all patients had suffered from rheumatoid arthritis for at least 8 years.

The diagnoses in the group of 165 individuals suffering from generalized osteo-arthritis, osteo-arthrosis, disk degeneration, or other rheumatic diseases are shown in Table IV (overleaf).

This group was mainly composed of patients referred to the rheumatic clinic, but included 27 persons who were seen in the course of a survey of relatives of patients with rheumatoid arthritis (Bremner, Alexander, and Duthie, 1959) and who were found to suffer from generalized osteo-arthritis, osteo-arthrosis, disk degeneration, or some minor rheumatic complaint.

The diagnoses in the 169 patients forming the group of miscellaneous diseases are shown in Table V (overleaf).

These patients had been referred to other units in the Northern Group of Hospitals with the exception of twelve who belonged to the group of relatives studied by Bremner, Alexander, and Duthie (1959). Whenever A.N.F. was detected, the diagnosis of D.L.E. or rheumatoid arthritis was definitely excluded, but mild osteo-arthrosis and disk degeneration might have been present. The 23 cases of erythema nodosum formed part of a group which was the subject of a report by Truelove (1960). These patients had had articular manifestations associated with a typical rash, but only one had signs of active disease at the time when serum was obtained.

The 580 control sera were obtained from 118 healthy relatives of patients suffering from rheumatoid arthritis and 462 blood donors about whom no information other than age and sex was available.

Titration of Anti-Nuclear Factor.—The presence of A.N.F. was demonstrated by a modification of the method previously described by Alexander and Duthie (1958), and Duthie, Bremner, and Alexander (1959).

Reagents

Human Leucocytes.—Blood was obtained by ear-prick and films were spread on standard microscope slides. The films were not fixed and were allowed to dry at room temperature. Films were used on the day of preparation. Leucocytes from a single healthy donor (Group B) were used throughout the investigation, although it had been established that results were the same if leucocytes from donors of other blood groups were substituted.

Serum.—Blood was obtained from patients and controls by venepuncture. The separated serum, if not used on the day of withdrawal, was stored at −15° C. The titre of A.N.F. was not affected by storage under these conditions. At the time of testing, serial eight-fold dilutions of serum in phosphate saline buffer (pH 7·0, 0·15 M) were prepared.

Fluorescent Anti-Human Globulin Serum.—Commercial anti-human globulin* (Coombs' serum) was conjugated with fluorescein isocyanate by the method of Coons and Kaplan (1950). Excess dye was removed from the serum by passage through a column containing an anionic exchange resin (De-acidite* FF (−200 + 400 mesh W.R. 1-1·5) in phosphate saline buffer. The fluorescein-conjugated anti-human globulin serum was then absorbed with sheep liver powder as described by Coons and Kaplan (1950). It was established that the conjugated antiserum did not impart fluorescence to the nucleus or cytoplasm of the untreated leucocytes used in the test.

* Burroughs Wellcome.

Method.—Each blood film was divided into four areas by marking the under-surface of the slide with a diamond. The test serum was applied undiluted and at 1/8, 1/64, and 1/512 to the four areas, care being taken to prevent the drops of individual dilutions coalescing. To minimize evaporation the preparation was placed in a covered Petri dish containing a pledget of moist cotton wool. After 30 minutes excess serum was washed from the slide with phosphate saline buffer. The preparation was washed further by immersing in phosphate saline buffer for 5 minutes and was then dried with a cloth, care being taken to leave untouched the areas of slide exposed to the test serum. To each area one drop of fluorescein-conjugated anti-human globulin was applied and the preparation was replaced in the Petri dish for 30 minutes at room temperature. The preparation was again washed in phosphate saline buffer and mounted in buffered glycerol at pH 7·0. Standard coverslips were used.

The preparations were examined in a fluorescence microscope modified in one respect from that described in detail by Alexander (1958). In the original microscope the specimen was mounted on a slide cut from Chance glass (OX7) which filtered all but ultraviolet and violet radiation from the exciting beam. In the present investigation it was impracticable to use such a slide in view of the large number of specimens examined. Standard microscope slides were therefore substituted and a filter to absorb visible radiation was placed between the source of U.V. light and the microscope. In early experiments a Wratten 18A filter,† which transmits U.V. radiation above 300 mμ was used (Duthie, Bremner, and Alexander, 1959). It was later shown, however, that a Wratten 18B filter, which transmits ultraviolet light over a wider waveband, provided a more intense excitation of the specimen with a corresponding increase in sensitivity of the technique. An 18B filter was therefore used throughout the present investigation.

Interpretation of Results.—The presence of green fluorescence on the nuclei of polymorph leucocytes was regarded as a positive result, and the titre of the serum was recorded as the highest dilution in which such fluorescence could be detected. Sera which were positive at a dilution of 1/512 were further diluted and retested so that an end-point could be recorded. Positive

* Permutit Co.
† Kodak Ltd

and negative sera were titrated with each batch of tests in order to standardize the sensitivity of the technique. The reproducibility of the method was tested by duplicate titrations of 110 sera. In 95 per cent. the results of the duplicate tests agreed, but in 5 per cent. divergent results were recorded. These divergences were most frequently observed in low titre sera.

Sensitized Sheep Cell Test (S.S.C.T.).—This was performed by the method of Ball (1950) modified as described by Duthie, Brown, Knox, and Thompson (1957). A titre of 1/128 was designated as the lowest positive titre in the test.

Haemoglobin (Hb) and Erythrocyte Sedimentation Rate (E.S.R.).—Venous blood was collected in Wintrobe's anticoagulant mixture. The haemoglobin concentration was measured by the alkali haematin method of Clegg and King (1942) in a photo-electric colorimeter. Results were expressed as a percentage of 14·8 g. Hb/100 ml. blood.

The E.S.R. was measured in Westergren tubes. The fall in mm. after 1 hour was recorded.

Functional Capacity.—This was assessed only in the patients suffering from rheumatoid arthritis, and was graded as follows:

I. Fit for all normal duties.

II. Moderate restriction (usual employment with modifications, light or part-time work; all housework except the heaviest; no dependency on others).

III. Marked restriction (only very light work; some degree of dependency on others).

IV. Confined to bed or chair (not capable of any work; completely dependent on others).

Results

Incidence of Anti-nuclear Factor

In Disseminated Lupus Erythematosus, Polyarteritis Nodosa, Scleroderma, and Dermatomyositis (Table III).—A.N.F. was detected in the serum of all patients suffering from D.L.E. and in ten of the twelve sera a titre greater than 1/64 was recorded. A.N.F. was also present in the serum of three patients suffering from polyarteritis nodosa and in that of one patient suffering from dermatomyositis. It was present in the serum of two of three patients with scleroderma. In this small series the incidence of A.N.F. was almost as high as in D.L.E., but the titre did not exceed 1/64 in any instance.

The S.S.C.T. was positive in five of the nineteen sera from patients in this group. A.N.F. was present in all five sera, but the titres were not related to the titres for sensitized sheep cells.

In Rheumatoid Arthritis.—A.N.F. was present in the serum of 65 per cent. of the 183 patients with rheumatoid arthritis. The titre was greater than 1/64 in twenty cases (11 per cent.). A detailed analysis of A.N.F. in relation to age, sex, duration of disease, haemoglobin, E.S.R., functional capacity, and the S.S.C.T. is presented in a later section of this report.

In Other Rheumatic Diseases (Table IV, overleaf). Serum was tested from 49 patients suffering from a polyarthritis conforming to the clinical and radiological pattern of generalized osteo-arthritis as described by Kellgren and Moore (1952). A.N.F. was present in eleven of the 49 sera (22 per cent.). The arthritis was associated with a raised E.S.R. in fourteen of the patients in this group. A.N.F. was present in the serum of four of these fourteen patients, and reached a titre of 1/64 in three instances.

There was evidence of co-existing disease in five of the 49 patients, but A.N.F. was not demonstrated in their serum.

A.N.F. was present in three of twenty sera (15 per cent.) from patients suffering from secondary osteoarthrosis. Of the three patients with a positive

Table III

INCIDENCE OF A.N.F. IN CLASSICAL "COLLAGEN DISEASES"

Diagnosis	A.N.F.						Total No. Tested	No. Positive
	Absent	Present (titre)						
		1/1	1/8	1/64	1/512	>1/512		
Disseminated lupus erythematosus	—	—	1	1	5	5	12	12
Polyarteritis nodosa	—	—	2	1	—	—	3	3
Dermatomyositis	—	—	—	1	—	—	1	1
Scleroderma	1	—	1	1	—	—	3	2
Total No. of Cases	1	0	4	4	5	5	19	18 (95 per cent.)

TABLE IV

INCIDENCE OF A.N.F. IN GENERALIZED OSTEO-ARTHRITIS, OSTEO-ARTHROSIS, DISK DEGENERATION, AND OTHER RHEUMATIC DISEASES

Diagnosis	A.N.F.						Total No. Tested	No. Positive	
	Absent	Present (titre)							
		1/1	1/8	1/64	1/512	>1/512		Total	Per cent.
Generalized osteo-arthritis ..	38	5	2	4	—	—	49	11	22
Secondary osteo-arthrosis	17	2	—	1	—	—	20	3	15
Disk degeneration	28	4	—	1	—	—	33	5	15
Ankylosing spondylitis	12	2	—	—	—	—	14	2	—
Psoriatic arthropathy	6	1	—	—	—	—	7	1	—
Arthritis (unclassified)	1	1	—	—	—	—	2	1	—
Gout	9	—	—	—	—	—	9	—	—
Rheumatic fever	8	—	—	—	—	—	8	—	—
Juvenile rheumatoid arthritis ..	7	—	—	—	—	—	7	—	—
Capsulitis, bursitis, and ligamentous strain	16	—	—	—	—	—	16	—	—
Total No. of Cases	142	15	2	6	0	0	165	23	—

test, however, one suffered concomitantly from congestive cardiac failure and another had swelling of one proximal interphalangeal joint but no other signs compatible with the diagnosis of rheumatoid arthritis or generalized osteo-arthritis. The titre of A.N.F. in the sera from these two patients was 1/64 and 1/1 respectively.

A.N.F. was demonstrated in five of 33 sera (15 per cent.) from patients in whom symptoms were attributed to degeneration of cervical or lumbar intervertebral disks. One patient, in whose serum A.N.F. was detected at a titre of 1/1, suffered also from a chronic infection of the upper urinary tract. In a further patient, about whom clinical data was incomplete, A.N.F. was present at a titre of 1/64.

A.N.F. was present in undiluted serum in two of fourteen patients with ankylosing spondylitis, in one of seven patients with psoriatic arthropathy, and in one patient suffering from a destructive arthritis of the hip joints of undetermined origin. A.N.F. was not demonstrated in gout, rheumatic fever, juvenile rheumatoid arthritis, or in patients presenting with non-articular lesions.

The S.S.C.T. was negative in all cases of generalized osteo-arthritis and secondary osteo-arthrosis, but was positive in one patient with disk degeneration. There was no clinical or radiological evidence of rheumatoid arthritis in this patient and A.N.F. was not present in her serum.

The S.S.C.T. was positive in two cases of juvenile rheumatoid arthritis, in one case of gout, and in one case of psoriatic arthropathy. A.N.F. was not detected in these four sera.

A proportion of the patients included within these diagnostic categories were relatives of patients suffering from rheumatoid arthritis. The incidence of A.N.F. was not affected by exclusion of the relatives from the analysis.

In Miscellaneous Diseases.—The incidence and titre of A.N.F. in relation to diagnosis in the group of 169 patients suffering from miscellaneous diseases is shown in Table V (opposite). A.N.F. was demonstrated in 17 per cent. of sera from this group, but in only two instances (1 per cent.) was the titre greater than 1/8. The number of patients in any single diagnostic category is too small for analysis.

The S.S.C.T. was positive in six of the 169 patients in this group (4 per cent.). There was no clinical evidence of rheumatoid disease in these patients and A.N.F. was not present in their serum.

In Controls.—The incidence and titre of A.N.F. in relation to age and sex in the control group is shown in Table VI (opposite). The incidence of A.N.F. did not differ between the sexes. It was detected in sera from 4 per cent. of males and females. In females A.N.F. was present in a higher proportion of sera from individuals belonging to the older age groups, but because of the small numbers in these groups the possible significance of this trend could not be established. In the 24 sera of both sexes in which A.N.F. was detected, the titre was greater than 1/8 in only one instance, and there was no evidence that titre was related to age.

The S.S.C.T. was performed in 553 of the 580 controls, and a positive test was recorded in eight of them (1 per cent.). Co-existence of A.N.F. and rheumatoid agglutinating factor occurred in only one serum, obtained from a woman of 61. She had previously complained of arthralgia, but no clinical or radiological evidence of arthritis was present at the time of examination.

TABLE V

INCIDENCE OF A.N.F. IN MISCELLANEOUS DISEASES

Diagnosis	A.N.F.						Total No. Tested	Total Positive
	Absent	Present (titre)						
		1/1	1/8	1/64	1/512	>1/512		
Pulmonary tuberculosis	4	3	—	—	—	—	7	3
Hamman-Rich syndrome	—	1	—	—	—	—	1	1
Chronic bronchitis	6	—	—	—	—	—	6	—
Other respiratory diseases	6	—	—	—	—	—	6	—
Congestive cardiac failure	2	1	1	1	—	—	5	3
Myocardial infarct	2	—	—	—	—	—	2	—
Cerebro-vascular lesion	3	—	—	—	—	—	3	—
Hypertension	1	—	—	—	—	—	1	—
Peptic ulcer	7	2	—	—	—	—	9	2
Hepatitis and cirrhosis	5	1	1	—	—	—	7	2
Cholecystitis and cholelithiasis	3	—	—	—	—	—	3	—
Crohn's disease	2	—	—	—	—	—	2	—
Other gastro-intestinal diseases	8	—	—	—	—	—	8	—
Hashimoto's disease	1	—	1	—	—	—	2	1
Hyperparathyroidism	2	—	—	—	—	—	2	—
Diabetes mellitus	3	—	—	—	—	—	3	—
Myxoedema	2	—	—	—	—	—	2	—
Other endocrine diseases	2	—	—	—	—	—	2	—
Disseminated sclerosis	7	—	—	—	—	—	7	—
Epilepsy	4	—	—	—	—	—	4	—
Viral encephalitis	2	—	—	—	—	—	2	—
Other neurological diseases	7	—	—	—	—	—	7	—
Erythema nodosum	18	2	3	—	—	—	23	5
Discoid lupus erythematosus	1	—	—	—	—	—	1	—
Carcinoma of breast	5	—	1	—	—	—	6	1
Other malignant disease	5	2*	—	—	—	—	7	2
Toxaemia of pregnancy	4	1	—	—	—	—	5	1
Other miscellaneous diseases	29	4†	2‡	—	1§	—	36	7
Total	141	17	9	1	1	—	169	28 (17%)

* Metastatic carcinoid tumour, Reticulosis } 2

† Cyst in breast, Schizophrenia, Pernicious anaemia, Purpura } 4

‡ Pyelonephritis, Anaemia of unknown origin } 2

§ Congenital heart disease, tuberculosis, and hyperparathyroidism

TABLE VI

RELATIONSHIP OF AGE AND SEX TO TITRE OF A.N.F. IN CONTROLS

Sex	Age Group (yrs)	A.N.F.				Total No. Tested	No. Positive	
		Absent	Present (titre)				Total	Per cent.
			1/1	1/8	1/64			
Male	0–24	62	2	—	—	64	2	3
	25–34	102	3	2	—	107	5	5
	35–44	81	4	—	—	85	4	5
	45–54	64	—	3	—	67	3	5
	55+	25	—	—	—	25	0	—
	Total	334	9	5	0	348	14	4
Female	0–24	59	1	—	—	60	1	2
	25–34	49	1	—	—	50	1	2
	35–44	61	2	—	1	64	3	5
	45–54	45	1	1	—	47	2	4
	55+	8	3	—	—	11	3	25
	Total	222	8	1	1	232	10	4
Total Both Sexes		556	17	6	1	580	24	4

ANTI-NUCLEAR FACTOR IN RHEUMATOID ARTHRITIS

Age and Sex (Table VII).—A.N.F. was present in the serum of 60 per cent. of males and 67 per cent. of females, and in both sexes the incidence was higher in the older age groups. This trend was more pronounced in males, but a true difference in pattern between the sexes could not be established because of the small numbers in the younger age groups.

The distribution of titres differed between the sexes. In females the peak incidence of positive tests occurred at a titre of 1/8 and not, as in males, in undiluted serum. No relationship between titre and age was apparent in females, but in males titres greater than 1/64 were recorded only in patients over the age of 55.

Duration of Disease (Table VIII).—The lowest incidence of A.N.F. (51 per cent.) was recorded in sera from patients who had suffered from rheumatoid arthritis for 8 to 10 years, the shortest duration available for analysis in this study. The incidence was directly related to duration of disease and A.N.F. was detected in 83 per cent. of patients in whom the duration of disease was 20 years or more. There was, however, no close association of high titres with long duration of disease.

Concentration of Haemoglobin (Table IX).—A.N.F. was present in the serum of all patients in

TABLE VII
RELATIONSHIP OF AGE AND SEX TO PRESENCE AND TITRE OF A.N.F.

Sex	Age Group (yrs)	A.N.F.						Total No. Tested	No. Positive	
		Absent	Present (titre)						Total	Per cent.
			1/1	1/8	1/64	1/512	>1/512			
Male	0–34	2	1	—	—	—	—	3	1	33
	35–54	10	2	1	2	—	—	15	5	33
	55+	6	9	6	3	2	1	27	21	77
	Total ..	18	12	7	5	2	1	45	27	60
Female	0–34	2	—	—	—	—	—	2	—	—
	35–54	17	7	10	10	3	2	49	32	65
	55+	27	15	18	15	9	3	87	60	69
	Total ..	46	22	28	25	12	5	138	92	67
Total Both Sexes		64	34	35	30	14	6	183	119	65

TABLE VIII
RELATIONSHIP OF DURATION OF DISEASE TO PRESENCE AND TITRE OF A.N.F.

Duration of Disease (yrs)	A.N.F.					Total No. Tested	No. Positive	
	Absent	Present (titre)					Total	Per cent.
		1/1	1/8	1/64	1/512 or Over			
8–10	23	8	5	6	5	47	24	51
10–15	27	12	13	12	5	69	42	61
15–20	8	9	6	4	4	31	23	74
Over 20	6	5	11	8	6	36	30	83
Total ..	64	34	35	30	20	183	119	65

TABLE IX
RELATIONSHIP OF HAEMOGLOBIN CONCENTRATION TO PRESENCE AND TITRE OF A.N.F.

Haemoglobin (% of 14·8 g.)	A.N.F.					Total No. Tested	No. Positive	
	Absent	Present (titre)					Total	Per cent.
		1/1	1/8	1/64	1/512 or Over			
Over 90	31	12	12	15	6	76	45	60
80–89	24	12	16	8	5	65	41	62
70–79	9	7	4	6	5	31	22	71
Under 70	—	3	3	1	4	11	11	100
Total ..	64	34	35	30	20	183	119	65

whom the haemoglobin concentration was less than 70 per cent., and a titre of 1/512 or higher was recorded in four of these patients (36 per cent.). The incidence of A.N.F. was lowest (60 per cent.) in patients with a haemoglobin of 90 per cent. or more and the titre was 1/512 or more in only six of 76 cases (8 per cent.).

Erythrocyte Sedimentation Rate (Table X).—A.N.F. was present in the serum of 80 per cent. of the forty patients in whom the E.S.R. was 60 mm./hr or greater, and in ten cases (25 per cent.) a titre of 1/512 or more was recorded. In the 44 patients with an E.S.R. of 19 mm./hr or less, A.N.F. was present in 48 per cent. The titre was 1/512 or more in only three of these patients (7 per cent.).

Functional Capacity (Table XI).—Sera from all patients confined to bed or chair (Grade IV) contained A.N.F. The incidence decreased among patients in the higher grades of functional capacity and A.N.F. was demonstrated in only 39 per cent. of patients fit for all normal activities (Grade I). No close relationship of titre of A.N.F. to the grade of functional capacity was found, the distribution of high titres of A.N.F. being similar in all four grades.

Sensitized Sheep Cell Test (Table XII).—The presence of A.N.F. was associated with a positive S.S.C.T. in 47 per cent. of males and 42 per cent. of females. Both tests were negative in 27 per cent. and 19 per cent. of males and females respectively. In 13 per cent. of males and 14 per cent. of females the sheep cell test was positive in the absence of A.N.F. A negative S.S.C.T. was associated with the presence of A.N.F. in the serum of 25 per cent. of females but in only 13 per cent. of males.

TABLE XII

RELATIONSHIP OF THE SENSITIZED SHEEP CELL TEST TO THE PRESENCE OF A.N.F., BY SEX

Sensitized Sheep Cell Test	Anti-nuclear Factor	Sex			
		Male		Female	
		No.	Per cent.	No.	Per cent.
Positive	Present	21	47	58	42
Positive	Absent	6	13	20	14
Negative	Present	6	13	34	25
Negative	Absent	12	27	26	19
Total		45		138	

TABLE X

RELATIONSHIP OF ERYTHROCYTE SEDIMENTATION RATE TO PRESENCE AND TITRE OF A.N.F.

Erythrocyte Sedimentation Rate (mm./1 hr)	A.N.F.					Total No. Tested	No. Positive	
	Absent	Present (titre)						
		1/1	1/8	1/64	1/512 or Over		Total	Per cent.
0–19	23	6	4	8	3	44	21	48
20–39	24	6	17	8	2	57	33	58
40–59	9	16	6	6	5	42	33	78
Over 60	8	6	8	8	10	40	32	80
Total ..	64	34	35	30	20	183	119	65

TABLE XI

RELATIONSHIP OF FUNCTIONAL CAPACITY TO PRESENCE AND TITRE OF A.N.F.

Grade of Functional Capacity	A.N.F.					Total No. Tested	No. Positive	
	Absent	Present (titre)						
		1/1	1/8	1/64	1/512 or Over		Total	Per cent.
I	25	3	4	5	4	41	16	39
II	28	17	19	12	9	85	57	67
III	11	8	7	10	5	41	30	73
IV	—	6	5	3	2	16	16	100
Total ..	64	34	35	30	20	183	119	65

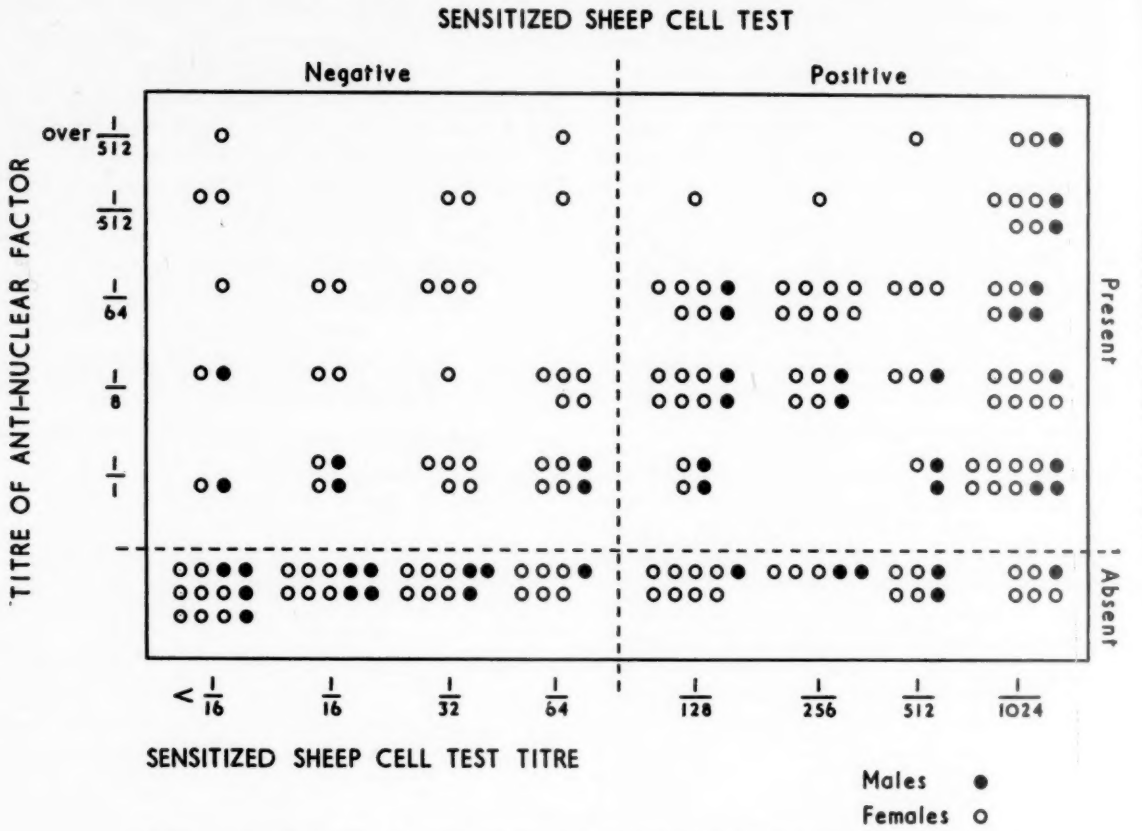

Figure.—Distribution of titres for sensitized sheep cell test and anti-nuclear factor in individual sera, by sex.

Titres of A.N.F. and rheumatoid agglutinating factor in individual patients are shown in the Figure. In the females no relationship between titres in the two tests was apparent, but in the males a titre of A.N.F. greater than 1/1 associated with a negative sheep cell test was recorded in only one instance.

Relationship of Anti-nuclear Factor and Sensitized Sheep Cell Test to Haemoglobin Concentration, Erythrocyte Sedimentation Rate, Functional Capacity, and Duration of Disease

In view of the probable influence of the S.S.C.T. on prognosis (Duthie, Brown, Knox, and Thompson, 1957) and the present finding of an association of A.N.F. with some of the manifestations of active rheumatoid disease, the status of patients, grouped according to the results of both serological tests, have been compared (Table XIII, opposite).

Irrespective of the result of the S.S.C.T., a haemoglobin of less than 70 per cent. was not recorded in patients with a negative test for A.N.F. The haemoglobin was above 90 per cent. in 58 per cent. of patients in whom both tests were negative, but exceeded 90 per cent. in only 35 per cent. of patients in whom a negative test for A.N.F. was associated with a positive S.S.C.T.

47 per cent. of patients in whom both tests were negative had a normal E.S.R. compared with 19, 23, and 15 per cent. in the other groups. E.S.R.s of 60 mm./hr or more were most frequently recorded in patients with a positive test for A.N.F., the highest percentage (32 per cent.) being recorded when the S.S.C.T. was also positive.

A similar trend was noted in respect of functional capacity. Where both tests were negative, 53 per cent. of patients were in Grade I and none was in Grade IV. No patient with a negative test for A.N.F. and a positive S.S.C.T. was in Grade IV, but only 19 per cent. were in Grade I. When both tests were positive only 9 per cent. of patients were in Grade I and 14 per cent. were in Grade IV.

The duration of disease was 8-10 years in 42 per cent. of patients in whom both tests were negative, and only 8 per cent. of such patients had had the disease for 20 years or more. Where, however, both tests were positive, the disease was of short duration in only 16 per cent. of patients, and exceeded 20 years in 27 per cent.

From this data, and in view of the increased incidence of A.N.F. in patients with long-standing disease, it seemed possible that low haemoglobin levels, raised E.S.R., and marked impairment of function might be more closely related to duration of disease than to the presence of serological abnormalities. This possibility

TABLE XIII

RELATIONSHIP OF A.N.F. AND S.S.C.T. TO HAEMOGLOBIN CONCENTRATION, ERYTHROCYTE SEDIMENTATION RATE, FUNCTIONAL CAPACITY, AND DURATION OF DISEASE

Test		No. of Patients	Haemoglobin (per cent.)			Erythrocyte Sedimentation Rate (mm./1 hr)			Functional Capacity (Grade)			Duration of Disease (yrs)			
A.N.F.	S.S.C.T.		90	70–89	<70	0–19	20–59	60+	I	II and III	IV	8–10	10–15	15–20	20+
—	—	38	58%	42%	—	47%	24%	13%	53%	47%	—	42%	34%	16%	8%
—	+	26	35%	65%	—	19%	57%	12%	19%	81%	—	27%	54%	7%	12%
+	—	40	43%	42%	15%	23%	33%	16%	23%	65%	12%	28%	28%	22%	22%
+	+	79	35%	58%	7%	15%	25%	32%	9%	77%	14%	16%	39%	18%	27%
Total		183													

was examined by further analysis of the serological groups subdivided in respect of duration of disease (Table XIV). The numbers in the individual categories were generally small, but are expressed in percentages to simplify comparison between groups.

The relationships between the serological findings and haemoglobin, E.S.R., and functional capacity were of the same pattern as that seen in Table XIII, and were not solely determined by the duration of disease.

Discussion

The results of this investigation suggest that A.N.F. is not specifically associated with the classical "collagen diseases" and rheumatoid arthritis, although as observed by Friou (1958a) it is present most frequently in these diseases and the highest titres occur in cases of D.L.E.

Previous workers have been mainly concerned

TABLE XIV

RELATIONSHIP OF A.N.F., S.S.C.T., AND DURATION OF DISEASE TO HAEMOGLOBIN CONCENTRATION, ERYTHROCYTE SEDIMENTATION RATE, AND FUNCTIONAL CAPACITY

Duration of Disease (yrs)	Test		No. of Patients	Haemoglobin (per cent.)			Erythrocyte Sedimentation Rate (mm./1 hr)			Functional Capacity (Grade)		
	A.N.F.	S.S.C.T.		90+	70–89	<70	0–19	20–59	60+	I	II and III	IV
8–10	—	—	16	75%	25%	—	58%	36%	6%	75%	25%	—
	—	+	7	43%	57%	—	15%	85%	—	30%	70%	—
	+	—	11	63%	28%	9%	18%	64%	18%	45%	45%	10%
	+	+	13	23%	69%	8%	15%	62%	23%	23%	62%	15%
	Total		47									
10–15	—	—	13	46%	54%	—	40%	45%	15%	23%	77%	—
	—	+	14	21%	79%	—	21%	65%	14%	14%	86%	—
	+	—	11	28%	63%	9%	28%	63%	9%	28%	44%	28%
	+	+	31	33%	60%	7%	12%	52%	36%	12%	74%	14%
	Total		69									
Over 15	—	—	9	44%	56%	—	44%	34%	22%	56%	44%	—
	—	+	5	60%	40%	—	20%	60%	20%	20%	80%	—
	+	—	18	39%	39%	24%	24%	52%	24%	6%	88%	6%
	+	+	35	43%	51%	6%	18%	52%	30%	—	88%	12%
	Total		67									
Total			183									

with A.N.F. in relation to this group of diseases, and little information about the incidence in other disorders is available. Friou (1958a) detected A.N.F. in less than 2 per cent. of sera from patients suffering from miscellaneous diseases. In a comparable group in the present study, A.N.F. was present in 17 per cent. of sera, and was also demonstrated in 4 per cent. of sera from apparently healthy individuals. The discrepancy between Friou's results and those reported here is likely to be due to differences in the sensitivity of the techniques used, as a proportionate difference in incidence in rheumatoid arthritis is observed. If this explanation is correct, and if more sensitive techniques can be devised, it seems possible that A.N.F. may eventually be shown to be a normal component of human serum which is increased in some diseases, amongst which D.L.E. and the other members of the "collagen" group, including rheumatoid arthritis, are most prominent.

In view of the small numbers in any single diagnostic category, the incidence of A.N.F. in individual diseases outwith this group cannot be established. No common factor was apparent in the 17 per cent. of patients whose serum contained A.N.F., but it is interesting, in view of the report of Weir (1959), that in several instances impairment of hepatic function may have been present. The incidence of A.N.F. in secondary osteo-arthrosis and in disk degeneration approached that recorded in the miscellaneous group of diseases. It should be noted, however, that in a proportion of the cases of osteo-arthrosis and of disk degeneration where positive tests were obtained, the patients were suffering from coincident disease and it was not possible to establish that the presence of A.N.F. was related to their skeletal disorder.

In generalized osteo-arthritis, A.N.F. was detected in 22 per cent. of patients in none of whom was there evidence of other disease. This observation, together with the high incidence of generalized osteo-arthritis among females and the distinct familial predisposition, suggests that this disease may be a diffuse disorder of connective tissue, more closely related to rheumatoid arthritis than to osteo-arthrosis of the secondary type.

A study of the relationship of the presence of A.N.F. to some of the features of rheumatoid arthritis has been reported by Duthie and others (1959). The incidence of A.N.F. was shown to be higher in females (51 per cent.) than in males (43 per cent.). No association of age or duration of disease with the presence of A.N.F. was demonstrated in females, but in males the incidence of A.N.F. was lowest (28 per cent.) in patients below the age of 45, and was 30 per cent. in patients in whom the disease was of less than 10 years' duration. These observations agree with the results of the present investigation within the limitations imposed by the small numbers in the younger age groups and the absence of patients in whom the duration of disease was less than 8 years. Duthie and others (1959) showed that A.N.F. occurred most frequently in the presence of anaemia, raised E.S.R., and low functional capacity. This relationship of A.N.F. to signs of systemic disease has been confirmed in the present study, but no quantitative correlation between the titre of A.N.F. and the degree of anaemia, E.S.R., or grade of functional capacity has been demonstrated.

In the earlier study, A.N.F. was present in 55 per cent. of patients in whom the S.S.C.T. was positive, but in only 29 per cent. of patients with a negative S.S.C.T. The corresponding figures in the current investigation were 75 per cent. and 51 per cent. respectively, the higher overall incidence being accounted for by the use of a more sensitive technique.

The probable prognostic significance of the S.S.C.T. has been discussed by Duthie and others (1957), who showed that a consistently positive test was associated with a more serious prognosis as assessed by functional capacity. The results of Duthie and others (1959) suggested that the presence of A.N.F. might also indicate a poor prognosis and it was postulated that, whereas A.N.F. was related to the systemic manifestations of disease, the rheumatoid agglutinating factor was more commonly present when inflammatory changes in the joints were prominent. The results of the present study confirm that both A.N.F. and rheumatoid factor may be of prognostic significance and that A.N.F. was more closely associated both with signs of active disease and with impaired functional capacity. A.N.F. was present in the serum of all patients in whom the Hb concentration was less than 70 per cent. and in that of all those who were in the lowest grade of functional capacity. The influence of the S.S.C.T. on these indices was less obvious, but, in general, a positive test, irrespective of the presence or absence of A.N.F., was associated with lower clinical status. Patients in whom both tests were negative generally fared better in all respects than their fellows. Although the incidence of A.N.F. was greater in patients with prolonged disease, the relationship to clinical status was maintained independently of duration of disease.

The almost universal occurrence of A.N.F. in the classical "collagen diseases" and its association with signs of systemic disturbance in rheumatoid arthritis

might suggest that the factor is closely linked with diseases in which diffuse inflammatory changes in connective tissue are prominent. A.N.F. has, however, been demonstrated in a number of sera from healthy individuals and in patients suffering from diseases such as osteo-arthrosis and disk degeneration in which there was no obvious evidence of inflammatory lesions.

It is possible that the A.N.F. demonstrated in D.L.E. may differ qualitatively from that present in rheumatoid arthritis and in other sera. It has been emphasized by Holman and Kunkel (1959) that, with techniques similar to those used in the present study, the homogeneity of A.N.F. cannot be established. Deicher, Holman, and Kunkel (1959) have shown that the serum in D.L.E. may contain several globulins with an affinity for tissue nuclei. A similar heterogeneity probably exists in other sera. It remains true, however, that these factors, although distinguishable one from another by special techniques, have the common property of combining with nuclear material and may be produced in response to similar stimuli. The demonstration of A.N.F., using the term in a generic sense, in a wide variety of human sera, suggests that the occurrence of the appropriate stimulus is not limited to D.L.E. or other "collagen diseases".

The stimulus to the production of A.N.F. remains unknown. The factor possesses the property of an antibody to nuclear material, but it has not been established that its production is due either to a derangement of the normal immune mechanism or to the presence of nuclear material degraded or altered to the extent that it is treated as an antigen by the cells normally responsible for synthesis of antibody. Degradation or alteration of nuclear material may follow dissolution of tissue, whether this be due to disease or to senescence of cells, and may provide the stimulus for production of A.N.F. This hypothesis is consistent with the concept of A.N.F. as a normal component of human serum, but it does not adequately explain the occurrence of large amounts of A.N.F. in the serum of patients suffering from D.L.E. and the high incidence of the factor in other "collagen diseases". Even if it should be established that A.N.F. is not of causal importance, the final explanation of its prevalence in these diseases may contribute to the understanding of their aetiology.

Summary

(1) A sensitive method for the detection and titration of anti-nuclear factor (A.N.F.) in human serum is described.

(2) The results in 1,116 sera are reported and compared with those obtained in previous investigations.

(3) Anti-nuclear factor was detected in the serum of all patients with disseminated lupus erythematosus. It was also present in three cases of polyarteritis nodosa, one case of dermatomyositis, and in two of three cases of scleroderma.

(4) Anti-nuclear factor was present in the serum of 65 per cent. of 183 patients with rheumatoid arthritis, 22 per cent. of 49 cases of generalized osteo-arthritis, 15 per cent. of twenty cases of secondary osteo-arthrosis, 15 per cent. of 33 cases of disk degeneration, 6 per cent. of 63 patients with other rheumatic conditions, 17 per cent. of 169 patients suffering from a variety of other diseases, and 4 per cent. of 580 apparently healthy individuals.

(5) In rheumatoid arthritis the incidence of anti-nuclear factor was highest among patients with signs of active disease (as indicated by the presence of anaemia and a rapid erythrocyte sedimentation rate) and among those with serious impairment of functional capacity. Severe disease was most common in patients in whom the presence of anti-nuclear factor was associated with a positive sensitized sheep cell test. Patients in whom both tests were negative had fared better in all respects than the remainder of the group.

(6) The possible significance of these results is discussed.

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Fréquence du facteur antinucléaire dans le sérum humain

RÉSUMÉ

(1) On décrit un procédé sensible pour dépister et titrer le facteur antinucléaire (A.N.F.) dans le sérum humain.

(2) On présente les résultats sur 1,116 sérums et on les compare avec ceux obtenus au cours des travaux antérieurs.

(3) On a décélé le facteur antinucléaire dans le sérum de tous les malades atteints de lupus érythémateux disséminé. Il était aussi présent dans trois cas de périartérite noueuse, un cas de dermatomyosite et en deux sur trois cas de sclérodermie.

(4) Le facteur antinucléaire était présent dans le sérum de 65% des malades atteints d'arthrite rhumatismale, 22% des 49 cas d'ostéoarthrite généralisée, 15% des 20 cas d'ostéoarthrite secondaire, 15% des 33 cas de dégénérescence discale, 6% des 63 cas d'autres affections rhumatismales, 17% des 169 sujets atteints d'autres maladies et de 4% des 580 sujets apparemment sains.

(5) Dans l'arthrite rhumatismale la fréquence du facteur antinucléaire était plus grande chez des sujets accusant des signes d'évolution morbide (indiquée par la présence d'anémie et une vitesse élevée de sédimentation érythrocytaire) et chez ceux dont la capacité fonctionnelle était gravement affectée. La maladie était le plus souvent sévère quand la présence du facteur antinucléaire s'associait à une agglutination positive des globules de mouton sensibilisés. Les malades chez qui les deux réactions étaient négatives allaient mieux de tous les points de vue que les autres dans le groupe.

(6) On discute l'importance possible des ces résultats.

Incidencia del factor antinuclear en el suero humano

SUMARIO

(1) Se describe un método sensible de detección y titulación del factor antinuclear (A.N.F.) en el suero humano.

(2) Se presentan los resultados en 1,116 sueros y se comparan con los obtenidos en investigaciones previas.

(3) Se detectó factor antinuclear en el suero de todos los enfermos con lupus eritematoso diseminado. Estaba presente también en tres casos de periarteritis nodosa, un caso de dermatomiositis y en dos de tres casos de esclerodermia.

(4) El factor antinuclear estaba presente en el suero del 65% de 183 enfermos con artritis reumatoide, 22% de 49 casos de osteoartritis generalizada, 15% de 20 casos de osteoartritis secundaria, 15% de 33 casos de degeneración discal, 6% de 63 enfermos con otros disturbios reumáticos, 17% de 169 enfermos padeciendo otras varias enfermedades y 4% de 580 individuos aparentemente sanos.

(5) En la artritis reumatoide la incidencia del factor antinuclear fué más elevada entre los sujetos con signos de evolución mórbida (indicada por la presencia de anemia y elevada velocidad de sedimentación eritrocitaria) y entre aquellos con seria afectación de la capacidad funcional. Un tipo severo de enfermedad ocurría cuando la presencia del factor antinuclear estaba asociada a una reacción positiva de aglutinación de los eritrocitos de carnero sensibilizados. Los enfermos en quienes ambas reacciones eran negativas están en todos los aspectos mejor que el resto del grupo.

(6) Se discute el posible significado de estos hallazgos.

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URICOSURIC AGENTS IN THE TREATMENT OF GOUT

BY

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During the past 2½ years an attempt has been made to assess the relative value and toxicity of various uricosuric agents.

Previous Investigations

Kersley, Cook, and Tovey (1958) reported the therapeutic value of G.28 315 (sulphinpyrazone), a phenylbutazone derivative now known as Anturan (Geigy), in a group of fifteen patients with gout in a clinical trial lasting 3 to 8 months. Benemid and Longacid (Urelim), a benemid-like drug (Ward, Blenkinsop and Co.), were also given in selected cases. The results, as shown by estimations of the urinary uric acid excretion and the serum uric acid, are summarized in the Table (Rows 1-4). Anturan was the most efficacious drug, although the other two also had a definite uricosuric effect. Intermittent administration 3 days per week was not effective. It was found that the use of 3·5 g. aspirin as an analgesic completely inhibited the effect of Anturan in the doses given (Table, Row 5).

Present Study

Material.—32 patients were all suffering from typical gout, with raised serum uric acid levels and normal differential agglutination tests. The average age was 56 years. The average age at onset was 41 years (range 22 to 71), fourteen being aged 25 to 35 years at onset. There were 27 men and five women. Thirteen patients gave a definite family history of gout.

Medication.—Each patient had a period on both Anturan and Urelim. Nine had Anturan and two Urelim continuously for more than a year, and the remaining 21 received the two drugs alternately. In eighteen cases Anturan and Urelim were tried together and separately, and in the same group a third drug, Zoxazolamine (Flexin; 2-amino-5-chlorobenzoxazole), was also tried separately.

The chemical structure of all these drugs is shown in the Figure.

In view of our previous finding that 3·5 g. aspirin given simultaneously with Anturan completely

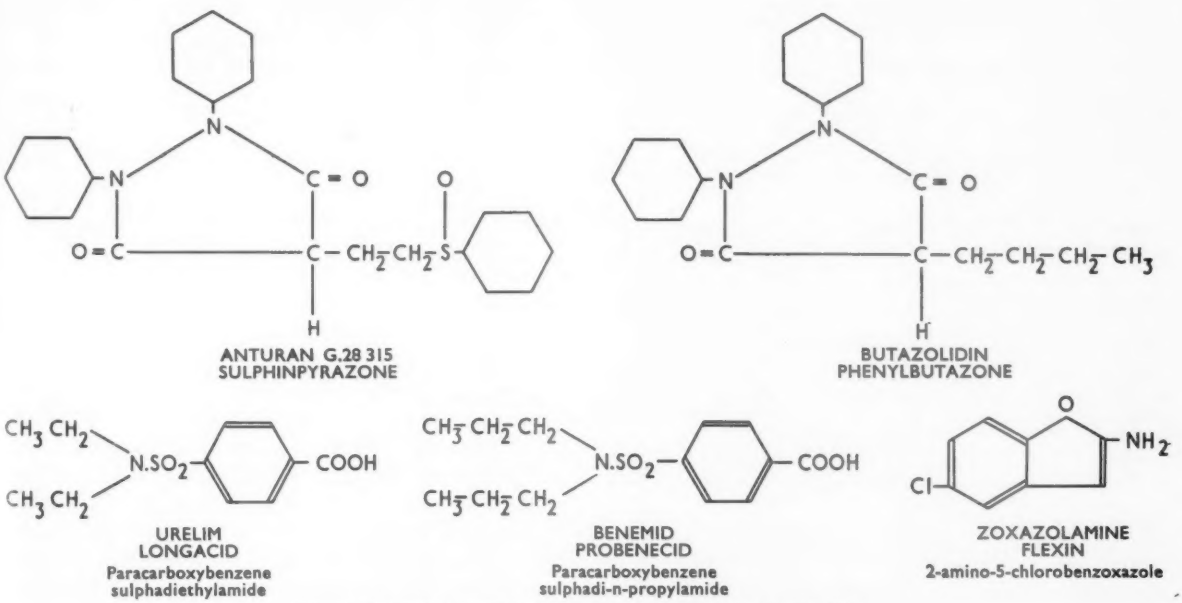

Figure.—Chemical formulae of uricosuric agents used in this trial.

inhibited the uricosuric effect of the latter, the results were observed of giving aspirin or paracetamol* to four patients who were taking Anturan regularly, and to one who was taking Zoxazolamine.

Further investigations included the effects of Anturan and Zoxazolamine on the serum cholesterol and prothrombin times.

Results

Anturan.—The patients who continued on Anturan continued to do well, the serum uric acid levels remaining the same at the end of one year as they had been at the end of 3 months. In the patients shown in the Table (Row 4) in whom the average serum uric acid level was 7·1 mg./100 ml. before treatment and 4·8 mg./100 ml. at the end of 3 months, the level was 4·9 mg./100 ml. after one year.

Anturan + Urelim.—Eighteen patients who were taking Anturan 400 mg. daily regularly for some months were given in addition 1·5 g. Urelim daily for one week, and the Urelim was continued at the same dosage for a further week while the Anturan was reduced to 200 mg. daily. The average daily serum uric acid level was 3·5 mg./100 ml. on Anturan alone, fell to 2·9 mg./100 ml. when Urelim was added, and rose to 3·1 mg./100 ml. when the Anturan was reduced (Table, Rows 7-9). Meanwhile, the average daily urinary uric acid excretion rose from 776 to 806, and then fell to 654 mg./100 ml. The results suggest that Urelim had an adjuvant effect in combination with Anturan.

Urelim.—This drug was also tried alone in seven patients, who received 1·5 g. daily. Their average urinary uric acid excretion (which had been 608 mg./day before treatment) rose to 880 mg./day, and the serum uric acid level (7·8 mg./100 ml. before treatment) fell to 6·4 mg./100 ml. (Table, Row 6). Thus Urelim was not so effective alone as with Anturan.

Panok, Panadol.

TABLE

RESULTS OF PREVIOUS INVESTIGATION AND PRESENT STUDY

Source	Drugs under Trial: Drug	Drugs under Trial: Dosage	No. of Cases in Group Tested	Before Start of Treatment: Urinary Uric Acid Excretion (mg./day)	Before Start of Treatment: Serum Uric Acid (mg./100 ml.)	Effects of Single Drug: Urinary Uric Acid Excretion (mg./day)	Effects of Single Drug: Serum Uric Acid (mg./100 ml.)	Effects of Drug or Drugs on Trial: Urinary Uric Acid Excretion (mg./day)	Effects of Drug or Drugs on Trial: Serum Uric Acid (mg./100 ml.)	
Kersley and others, 1958 (Tables I-IV)	Benemid (I and II)	1·5 g.	7	581	7·6	825 ($p < 0·01$)	5·2			(1)
	Anturan (I and II)	400 mg.	13	551	7·8	880 ($p < 0·01$)	4·0			(2)
	Anturan (I)	800 mg.	7	581	7·6	1,042 ($p < 0·001$)				(3)
	Anturan for 3 months (III)	400 mg.	7	540	7·1	828	4·8*			(4)
	Anturan + Aspirin (IV)	3·5 g.	9	576	7·7	947	4·8	401	4·8	(5)
Results of Present Study	Urelim	1·5 g.	7	608	7·8	880	6·4			(6)
	Anturan	400 mg.	18			776	3·5			(7)
	Anturan + Urelim	400 mg. 1·5 g.	18					806	2·9	(8)
	Anturan + Urelim	200 mg. 1·5 g.	18					654	3·1	(9)
	Zoxazolamine	1·5 g.	18					712	3·3	(10)
	Anturan + Aspirin	400 mg. 3·5 g.	4			770		637		(11)
	Zoxazolamine + Aspirin	1·5 g. 3·5 g.	1			808	1·9	580	3·8	(12)
	Anturan + Paracetamol	400 mg. 3·5 g.	4			770	3·3	756		(13)

* 4·9 after 1 year.

Zoxazolamine.—This drug was originally produced as a relaxant, depressing the subcortical and spinal pathways (*Lancet*, 1956). A dose of 0·25 g. was said to promote uricosuria by Burns, Yü, Berger, and Gutman (1958) and Reed, Feichtmeir, and Willett (1958), and its effect was therefore compared with that of Anturan and Urelim. The same eighteen patients who had been taking Anturan 400 mg. daily regularly for some months were given Zoxazolamine 1·5 g. daily for one week. The average daily serum uric acid level fell from 3·5 to 3·3 mg./100 ml., but at the same time the average daily urinary uric acid excretion fell from 776 to 712 mg. (Table, Row 10).

Addition of Analgesics

Aspirin.—Four patients who were taking Anturan 400 mg. daily regularly were given 3·5 g. aspirin in addition, and the average daily urinary uric acid excretion fell from 770 to 637 mg. (Table, Row 11).

One patient who had taken Zoxazolamine 1·5 g. for one week was given 3·5 g. aspirin in addition for a further week, and the daily urinary uric acid excretion fell from 808 to 580 mg., while the serum uric acid level rose from 1·9 to 3·8 mg./100 ml. (Table, Row 12).

Paracetamol (N-acetyl-p-amino-phenol; Panadol, Panok).—The four patients on Anturan who had been tested with additional aspirin were also tested with additional paracetamol 3·5 g. daily, and the average daily urinary uric acid excretion fell only very slightly from 770 to 756 mg. (Table, Row 13).

The question of analgesics is important in a case presenting both gout and osteo-arthritis, and it appears that paracetamol can be combined with a uricosuric agent without significantly inhibiting the effect of the latter.

Effect of Uricosuric Agents on Blood Coagulation and Serum Cholesterol.

Thompson, Mikkelsen, and Willis (1959), who reviewed the uricosuric effect of various anticoagulants, found that ethylbicoumacetate (Tromexan), bihydroxycoumarin, and anisindione produced uricosuria.

Kohn and Prozan (1959), who found that a series of patients with acute myocardial infarction had serum uric acid levels above 6 mg./100 ml., suggested that the exhibition of uricosuric drugs might afford some protection against coronary atherosclerosis.

Gertler and White (1954) has suggested that high serum uric acid levels might encourage the deposition of cholesterol, so that a lowering of the serum uric acid level might improve the prognosis by counteracting this process.

Serum cholesterol levels and prothrombin times were estimated in our gouty patients while under treatment with uricosuric agents.

Serum Cholesterol.—There is a wide variation in normal levels which average about 200 mg. per cent., the range according to Juergens and Achor (1959) being 150-250 mg. per cent. Treatment by restriction of fats and the use of oestrogens or thyroid extract has been advised for patients with levels above 250 mg. per cent.

Our eighty serum cholesterol estimations showed no direct correlation between the levels of cholesterol and uric acid. In thirty estimations on patients in whom the average serum uric acid level was below 3·5 mg./100 ml., the average serum cholesterol was 241 mg. per cent., and in twelve estimations on patients in whom the average serum uric acid level was above 4·5 mg./100 ml., the average serum cholesterol was 232 mg. per cent. In four cases for which figures were available before and after treatment, however, there was a tendency for the serum cholesterol to fall as the serum uric acid fell:

Case No.	Serum Uric Acid (mg./100 ml.)		Serum Cholesterol (mg. per cent.)	
	Before	After	Before	After
1	7·3	3·6	210	200
2	5·2	2·8	284	225
3	7·9	4·5	225	195
4	4·2	3·4	230	198

The average serum cholesterol in eighteen cases was 250 mg. per cent. before treatment, 242 after Anturan, and 219 after Zoxazolamine.

Prothrombin Time.—Eighty estimations (shown as a percentage of the pre-treatment time) were carried out on the eighteen patients who were treated with Anturan and Zoxazolamine; the average was 99 per cent. after Anturan and 97 per cent. after Zoxazolamine. When series of estimations carried out on individual patients were reviewed, there appeared to be a slight initial fall when the patient first took Zoxazolamine, followed by a rapid return to normal within a week or two in the majority of cases.

Subject Improvement and Side-Effects

All patients claimed that they had improved rather than deteriorated during the 2 years, in that

they were now having fewer attacks of gout and often had less general stiffness.

Eleven patients preferred Anturan. The reason was that they felt less "tired" and had less general stiffness and interval pain, probably because of the slight anti-inflammatory effect of this preparation.

Two patients preferred Urelim. One had developed boils while taking Anturan, but the white cell count remained normal and the boils did not recur on re-administration of Anturan. The other thought he had fewer attacks of gout while taking Urelim.

Of 21 patients who were transferred from Anturan to Zoxazolamine, five stated that they felt a "little tired" while taking the Zoxazolamine, one felt "muzzy" during the first 3 days of treatment, and one had slight headaches. Eight were equally well with either drug, but ten preferred Anturan and three Zoxazolamine.

Two patients had slight dyspepsia, but not sufficient to make one consider stopping medication during a minimum period of 6 weeks.

Course of the Disease

During the first 6 weeks of treatment there was a tendency to increase in the frequency of attacks of gout, but after this period there was marked lessening of frequency and severity. During this first 6 weeks, colchicine 0·5 mg. was given three times a day, and, if in spite of this, attacks occurred, phenylbutazone 600 mg. daily for 2 days was always completely successful in checking them.

In six instances there was a definite softening or decrease in the size of the tophi, and two patients reported some change in this direction after only 6 weeks' therapy.

Summary

32 patients with typical gout have been observed during treatment with uricosuric agents for at least 2 years, in continuation of the studies reported by Kersley and others (1958).

Anturan and Urelim were found to have a satisfactory effect both alone and in combination, and a similar effect was produced by the administration of Zoxazolamine.

Aspirin inhibited the uricosuric effect of all these drugs, but paracetamol did not do so.

Estimations were also made of the serum cholesterol and prothrombin times, with the idea of testing the theory that serum cholesterol and uric acid levels are related.

All the patients treated felt subjective benefit, although some felt better on one drug, and some on another. Toxic effects were rare and extremely slight, but on the whole Anturan was the favourite drug and the least toxic.

Because the numbers of patients who could be tested with each drug varied, and only a few could be observed daily for months in hospital, these results cannot collectively be subjected to statistical analysis. They show clearly, however, the great value, potency, and safety of the newer uricosuric drugs in the treatment of gout, with perhaps Anturan leading the field. Further work is required on the combined use of these drugs—*e.g.* the potentiation of Anturan by Urelim—and in particular on the degree of inhibition exerted by various dosages of other drugs, especially of the aspirin type. The possible importance of dosage inhibition is emphasized by the recent paper of Yü and Gutman (1959).

We are indebted to Dr. W. S. Stoddart of Messrs. Geigy Pharmaceutical Co. Ltd. for supplying the Anturan, to Dr. J. M. Simister of Messrs. Ward Blenkinsop and Co. for the Urelim, and the McNeil Laboratories Inc. of Philadelphia for the Zoxazolamine.

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Agents uricosuriques dans la goutte

RÉSUMÉ

A la suite des travaux rapportés par Kersley, Cook, et Tovey (1958), on a observé 32 malades atteints de goutte classique et traités par des agents uricosuriques pendant au moins deux ans.

Anturan et *Urelim* ont donné des résultats satisfaisants, aussi bien seuls qu'en combinaison, et on a obtenu un effet similaire avec *Zoxazolamine*.

L'aspirine inhibait l'effet uricosurique de tous ces produits, mais le paracetamol ne l'inhibait pas.

On a procédé aussi à des déterminations du cholestérol sérique et du temps de prothrombine, pour vérifier la théorie qu'il y avait un rapport entre les taux de cholestérol sérique et d'acide urique.

Tous les malades traités ont accusé une amélioration subjective, bien que certains d'entre eux en préféraient un produit à un autre. Des effets toxiques étaient rares et légers; en général, l'*Anturan* était le favori et le moins toxique.

Comme le nombre de malades traités par chaque produit variait et peu d'entre eux pouvaient être observés tous les jours pendant des mois à l'hôpital, ces

résultats, collectivement, ne se prêtent pas à l'analyse statistique. Ils montrent, toutefois, clairement la grande valeur, le pouvoir et l'inocuité des agents uricosuriques plus récents dans le traitement de la goutte, avec l'*Anturan* peut être à leur tête. D'autres travaux sont nécessaires sur l'emploi combiné de ces produits—par exemple la potentiation de l'*Anturan* par l'*Urelim*—et, en particulier, sur le degré d'inhibition exercée par des doses différentes de certains médicaments, surtout ceux du type de l'aspirine. L'importance possible de la dose dans l'inhibition a été soulignée récemment par l'article de Yü et Gutman (1959).

Agentes uricosúricos en la gota

SUMARIO

Como una continuación de los estudios presentados por Kersley, Cook, y Tovey (1958) se han observado 32 enfermos con cuadro típico de gota en tratamiento con agentes uricosùricos por lo menos durante dos años.

Resultados satisfactorios se apreciaron con *Anturan* y *Urelim*, administrados solos o en combinación, y un efecto similar se produjo con Zoxazolamine.

La aspirina inhibe el efecto uricosùrico de estos productos, lo que no sucede con el paracetamol.

Se realizaron también determinaciones de colesterol sérico y tiempo de protrombina, con la idea de comprobar la teoría de la relación entre los niveles de colesterol sérico y ácido ùrico.

Todos los enfermos tratados experimentaron mejoría subjetiva, aunque algunos la apreciaron más con un determinado fármaco mientras que otros reaccionaron mejor a otro diferente. Efectos tóxicos fueron raros y leves, en general. *Anturan* fué el más preferido y menos tóxico.

Como el nùmero de enfermos tratados con cada fármaco varió, y solamente unos pocos pudieron ser observados diariamente durante meses en hospital, estos resultados no se pueden someter colectivamente a análisis estadístico. De todas formas, es claramente manifesto el gran valor, la potencia y la inocuidad de los ùltimos agentes uricosùricos introducidos en la terapéutica de la gota, con el *Anturan* quizá a la cabeza de ellos. Es necesario más trabajo sobre el uso combinado de estos productos (p.e. la potenciación del *Anturan* por el *Urelim*), y particularmente sobre el grado de inhibición ejercida por diferentes dosis de otros fármacos, especialmente del tipo de la aspirina. La posible importancia de la dosis en inhibición es subrayada por el reciente trabajo de Yü y Gutman (1959).

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NEW URICOSURIC AGENT IN THE TREATMENT OF GOUT

para-CARBOXYBENZENESULPHA-DIETHYLAMIDE (URELIM)

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Several uricosuric drugs are now available for the long-term management of gout, the principal being aspirin, probenecid (Benemid), and sulphinpyrazone (Anturan). Recently two further drugs, Zoxazolamine (Flexin) and p-carboxybenzenesulpha-diethylamide (Urelim), have been introduced. Reed, Feichtmeier, and Willett (1958) commented on the uricosuric properties of Zoxazolamine, and drew attention to the numerous, albeit rarely serious, side-effects. To be effective in the treatment of gout, aspirin must be administered in large doses which may not be tolerated or may provoke toxic reactions. Probenecid is known to cause severe gastritis and rashes in some patients, and may occasionally cause hypersensitivity reactions. Sulphinpyrazone has been shown to carry the same risk of peptic ulceration as phenylbutazone in the rat (Domenjoz, 1960), and it is not unlikely that some of the other side-effects encountered with phenylbutazone may also occur with sulphinpyrazone, *e.g.* rashes and occasional blood dyscrasias.

The only published information concerning Urelim in the treatment of gout is a mention by Kersley, Cook, and Tovey (1958) of a comparison of this drug, then known as "Longacid", with sulphinpyrazone. They found that a dosage of 1 to 2 g. daily of Urelim resulted in an increased output of uric acid, but in only three out of eleven patients tested was the uricosuric effect equal to that obtained from 400 mg. sulphinpyrazone daily. Four patients reported drowsiness while taking Urelim, but no other side-effects were noted.

The present report is concerned with an evaluation of Urelim therapy in six patients studied in detail. Five of them suffered from primary gout and one had gout secondary to polycythaemia vera. Information was sought concerning the value of Urelim as a uricosuric agent, its dosage and optimum method of administration, effect on the serum uric acid level and the course of the illness, and any possible toxic or undesirable side-effects. The effect of aspirin given in combination with Urelim was also investigated. Only one patient was admitted to hospital during the period of investigation.

All patients were allowed a normal diet with adequate fluids, excluding only foods with a high purine content. All urine passed during the period of observation was collected in 24-hr samples, and the volume, uric acid, and creatinine contents were measured. The determination of volume and creatinine served as a check on the efficiency of collection. Serum uric acid was determined by a modification of Benedict's method, and blood urea and creatinine levels were also estimated at frequent intervals. Haemoglobin and white blood cell counts were also determined before and during the treatment periods. Special care was taken to ensure that no drugs with uricosuric effect, other than those prescribed, were administered during these studies. To simplify the presentation of results only mean values of uric acid excretion and serum uric acid are given for the various control and treatment periods. A minimum of 3 days' urine collection was required for a control period (*i.e.* without any uricosuric drug) and for the comparison of different

drugs. When a patient changed from one uricosuric agent to another, urine collections continued without interruption, but the results in the 24-hr specimen immediately after the change-over were omitted from the calculations of the mean uric acid excretion. Urelim was supplied in the form of white insoluble tablets without any characteristic taste, containing 500 mg. p-carboxybenzenesulphadiethylamide.

Case Reports

Case 1, a male student aged 22 years, who had a history of asthma and duodenal ulcer, developed acute gout on July 4, 1960, and successive serum uric acid levels were 8·5, 8·4, and 9·5 mg. per 100 ml., before he was started on Urelim. The subsequent findings and clinical course are shown in Table I. The acute attack of gout which supervened after Urelim and probenecid therapy was relieved by a short course of phenylbutazone.

Case 2, a retired steel worker aged 68 years, had a history of recurrent attacks of gouty arthritis for 10 years. The last major attack was in May, 1960, and after treatment with colchicine and probenecid he was given delta-butazolidin. This was discontinued on July 20, 1960, and after a control period of 5 days without any treatment, the patient started Urelim therapy. His gout remained quiescent throughout the period of investigation. The findings are summarized in Table II.

Case 3, a retired shopkeeper aged 66 years, had suffered from polycythaemia vera for 12 years and had developed gout in several joints in his hands and feet since 1956. He had been given colchicine tablets and probenecid intermittently since then and had taken probenecid 2 g. daily for 3 months before having a short trial of Urelim therapy. This patient also suffered from the mild residual effects of a left cerebral thrombosis, and observations were limited as he was treated at home. The findings are summarized in Table III.

TABLE III
OBSERVATIONS IN CASE 3

Medication	Probenecid 2 g.	Urelim 2 g.
Duration (days)	5	4
Mean Serum Uric Acid (mg./100 ml.)	8·1	9·4
Mean 24-hr Uric Acid Output (mg.)	747	1,066

TABLE I
OBSERVATIONS IN CASE 1

Medication	Control	Urelim 500 mg.	Urelim 1 g.	Benemid 1 g.	Benemid 1 g. + Urelim 1 g.	Urelim 1 g.	Control	Urelim 1·5 g.
Duration (days)	5	3	5	17	5	20	5	12
Mean Serum Uric Acid (mg./100 ml.)	9·5	9·6	10·7	6·3	5·3	—	12·0	8·0
Mean 24-hr Uric Acid Output (mg.)	672	861	857	1,529	43	778	—	—
Clinical Course	Mild gouty arthritis	Symptom free	No signs of gout	Mild dyspepsia	Increased dyspepsia	No dyspepsia but acute asthma and gout*	Symptom free	Symptom free

* Acute gout relieved by phenylbutazone 600 mg. for 3 days.

TABLE II
OBSERVATIONS IN CASE 2

Medication	Control	Urelim 1 g.	Urelim 2 g.	Sulphinpyrazone 300 mg.	Urelim 2 g. + Sulphinpyrazone 300 mg.	Urelim 2 g.	Urelim 1 g.	Urelim 1 g. + Aspirin 4·8 g.	Urelim 2 g. + Aspirin 4·8 g.	Urelim 3 g.
Duration (days)	5	8	6	6	6	5	25	10	5	5
Mean Serum Uric Acid (mg./100 ml.)	8·4	7·1	5·4	4·8	5·8	8·7	7·5	10·4	9·0	8·6
Mean 24-hr Uric Acid Output (mg.)	179	238	271	20	164	190	225	365	280	235

Case 4, a bus driver aged 47 years, had suffered from recurrent attacks of gouty arthritis in his knees and feet for 13 years. He had not obtained relief from previous aspirin therapy nor from probenecid. Sulphinpyrazone (Anturan) had been effective and he had taken 400 mg. daily for nearly 1 year, the only side-effects being recurrent mild renal haemorrhages without evidence of nephrolithiasis. After a control period of observation while on sulphinpyrazone therapy, the patient started Urelim on August 12, 1960. The subsequent findings are summarized in Table IV.

TABLE IV

OBSERVATIONS IN CASE 4

Medication ..	Sulphin-pyrazone 400 mg.	Urelim 2 g.	Sulphin-pyrazone 400 mg. + Urelim 2 g.	Urelim 1·5 g.
Duration	Nearly one year	5 days	6 days	28 days
Mean Serum Uric Acid (mg./100 ml.)	6·3	6·6	4·0	6·8
Mean 24-hr Uric Acid Output (mg.)	672	440	183	250

Case 5, a commercial traveller aged 54 years, had suffered from recurrent attacks of gout for 19 years, and had received intermittent treatment with colchicine and probenecid. He was admitted to hospital on July 1, 1960, because of an acute attack of gout and this responded partially to treatment with colchicine. After a control period, he started Urelim therapy on July 22, 1960. He sustained an acute exacerbation of gouty arthritis after 12 days of Urelim therapy, but this responded to phenylbutazone 600 mg. for 3 days. Further findings and the effect of 10 days combined treatment with aspirin and Urelim are shown in Table V.

Case 6, a housewife aged 72 years, had suffered from chronic tophaceous gout for 18 years. She had mild continuous joint pains in her hands and feet and some of the tophi had ulcerated. She could not tolerate aspirin in large dosage and previous therapy with probenecid had provoked violent hypersensitivity reactions on several occasions. A control serum uric acid level was 9·8 mg. on September 24, 1960, and she then started Urelim therapy, 0·5 g. daily for 7 days increasing to 1 g. daily for 10 days. Tabs. colchicine B.P. gr. 1/120 were given concurrently and she was found to be able to take Urelim with no side-effects.

Discussion

In three patients (Cases 1, 2, and 5) it was possible to obtain a direct measurement of the uricosuric effect of Urelim after a control period.

In Case 1, the uric acid output was raised by 28 per cent. during treatment with Urelim 0·5 g. daily and there was no greater output when the dosage was increased to 1 g. daily (Table I).

Case 2 showed an increase of 33 per cent. uric acid output on 1 g. Urelim daily and 51 per cent. when the dosage was raised to 2 g. (Table II).

Case 5 showed an increased uric acid output of 46 per cent. when given 1 g. Urelim daily (Table V).

These results support the claim that Urelim is a potent uricosuric agent, and indicate that 1 g. daily will increase the uric acid output by as much as 28 to 46 per cent. Increasing the Urelim dosage (from 0·5 to 1 g. daily) did not result in an increase in uric acid excretion in Case 1; this was probably due to the fact that this patient took the daily dosage of two tablets both together. This induced slight and transient drowsiness which later ceased when he took the drug in divided doses. It seems advisable that the Urelim dosage should be distributed throughout the day, in keeping with the recommended method of administration of other uricosuric agents, *e.g.* probenecid (Brøchner-Mortensen, 1958) and sulphinpyrazone (Kersley and others, 1958).

Urelim was well tolerated by all the patients in this series and during the short periods of treatment, ranging from 9 to 72 days, no serious side-effects occurred. As already mentioned, one patient (Case 1) noted slight and transient drowsiness about 4 hours after taking 1 g. Urelim, but he has sub-

TABLE V

OBSERVATIONS IN CASE 5

Medication	Control	Urelim 1 g.	Urelim 1 g. + Phenylbutazone 600 mg.	Urelim 1 g.	Urelim 2 g.	Urelim 2 g. + Aspirin 4·8 g.	Urelim 2 g.
Duration (days)	4	9	3	5	5	10	21
Mean Serum Uric Acid (mg./100 ml.)	6·5	5·4	6·7	5·0	4·0	8·8	6·5
Mean 24-hr Uric Acid Output (mg.)	317	462	633	372	—	418	—
Signs of Gout	+	+	+++	0	0	0	0

sequently taken 500 mg. three times daily without any recurrence of this symptom. Case 4 had a mild urticarial rash while taking 2 g. Urelim daily, but this subsided while he continued to take this drug and it has not recurred after a further 37 days of treatment with 1·5 g. daily. This patient had previously been subject to urticaria.

Even in this small series, three of the six patients were not able to tolerate other uricosuric drugs and Urelim assumed an important place in treatment. Case 1 could not take aspirin because of a duodenal ulcer, probenecid provoked dyspepsia, and sulphinpyrazone was not advocated because of gastro-intestinal risks, but Urelim has been administered for 37 days with no dyspeptic symptoms. Case 4 could not tolerate aspirin, probenecid had not helped him previously, and sulphinpyrazone had provoked haematuria, but he has taken Urelim for 60 days with no upset other than the mild urticarial rash which was not necessarily due to Urelim. Case 6 had previously experienced severe hypersensitivity reactions, with malaise, rash, and vomiting, on the several occasions on which she had attempted to take probenecid, and large doses of aspirin were not tolerated, but she was able to take 1 g. Urelim daily without upset. No significant alterations in white blood cell counts were noted during the periods of observation in these six patients.

The short-term effects of a uricosuric agent are not so evident in changes in the serum uric acid level as in the urinary uric acid output, and with small doses of aspirin the serum uric acid level may rise even though the urinary uric acid excretion rises (Brøchner-Mortensen, 1958). There were four patients in our series in whom the effect of Urelim on the serum uric acid level was observed. In Case 1 the serum uric acid level rose from 9·5 to 9·6 mg./100 ml. on 0·5 g. Urelim daily, and from 9·6 to 10·7 mg./100 ml. on 1 g. Urelim daily, even though the urinary uric acid output had increased (Table I). Case 2 showed a fall in the serum uric acid level from 8·4 to 7·1 mg./100 ml. on 1 g. Urelim daily, and from 7·1 to 5·4 mg./100 ml. on 2 g. Urelim daily, this being associated with successive increases in urinary uric acid output (Table II). Case 5 also showed a steady fall from 6·7 to 4·0 mg./100 ml. on 1 g. Urelim (Table V) and this was correlated with increased urinary uric acid output. Case 6 received only a small dosage of 0·5 g. Urelim daily for 1 week increasing to 1 g. daily for 10 days, and the serum uric acid level fell from 9·8 to 8·8 mg./100 ml.

From present data it can be said that Urelim is an effective uricosuric drug. The question of the potency of Urelim milligram for milligram in comparison with probenecid and sulphinpyrazone is of little moment. The important points concerning a drug are whether it is effective and whether it can be taken without undesirable side-effects, and short-term studies suggest that Urelim meets these requirements.

In view of the known inhibiting effect of salicylate upon the uricosuric actions of probenecid (Brøchner-Mortensen, 1958) and sulphinpyrazone (Ogryzlo and Harrison, 1957), and in view of the widespread use of analgesics containing aspirin, it seemed advisable to investigate the influence of aspirin upon the uricosuric effect of Urelim. Aspirin in a dosage of 4·8 g. (72 gr.) daily was administered to Cases 2 and 5. In both patients the serum uric acid levels rose quickly and appreciably, but there was little effect on the urinary uric acid output. These findings suggest that patients receiving Urelim should be advised to avoid analgesics containing aspirin.

We have studied the effect of some of these drugs in combination and in sequence. There was a dramatic fall in urinary uric acid output when a patient was transferred immediately from 2 g. Urelim to 300 mg. sulphinpyrazone daily (Table II). The combinations of Urelim and probenecid (Table I), and of Urelim and sulphinpyrazone (Table IV) led to marked reduction in urinary uric acid output. These preliminary findings could be of importance in the treatment of gout, and further studies are in progress.

It is generally sound advice for patients receiving uricosuric therapy to have an adequate fluid intake, as crystalluria may cause irritation, haemorrhage, and even renal damage. This is especially liable to occur with powerful uricosuric drugs where the margin of safety between therapeutic and excessive dosage may be small. Especial caution is necessary when the patient is known to have renal calculi.

None of the patients in this series suffered any genito-urinary side-effects when receiving Urelim, and renal function, estimated by serial determinations of creatinine clearance, remained unaltered during treatment.

There is the risk, common to all uricosuric drugs, of provoking an exacerbation of gout during the early stages of treatment, and uricosuric drugs are not prescribed for treatment of the acute gouty attack. One patient in this series (Case 5) suffered an acute attack of gout after taking Urelim for 10 days, and Case 1 also had an acute attack of gout, but this may have been precipitated by the preceding asthma rather than by the Urelim or probenecid he had taken. It is thought advisable that patients

starting Urelim therapy should receive a maintenance dosage of colchicine during the first 6 weeks of treatment.

Summary

The effect of a new uricosuric agent, p-carboxybenzenesulpha-diethylamide (Urelim), has been studied in six patients suffering from gout. It was found to be effective and well tolerated in doses ranging from 500 mg. to 2 g. daily. The only side-effect noted was drowsiness in one patient when a single dose of 1 g. was taken. Two patients who had side-effects with probenecid were able to take Urelim in effective dosage without trouble. Urelim would appear to be useful in the interval treatment of gout. As with other uricosuric drugs, Urelim may provoke acute gouty attacks in the early stages of treatment, and colchicine should be given during the first 6 weeks of treatment.

Comparison has been made between Urelim and other uricosuric drugs, and the effects of Urelim taken in combination with these drugs are also being studied.

We wish to thank Dr. J. M. Simister of Messrs' Ward, Blenkinsop & Co., for supplies of Urelim used in these studies. We also gratefully acknowledge the technical assistance of Mr. J. Watson and Miss P. Ord.

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Agent uricosurique nouveau dans le traitement de la goutte: p-carboxybenzènesulphadiethylamide (Urelim)

Résumé

On étudia chez six malades atteints de goutte l'effet d'un agent uricosurique nouveau, p-carboxybenzènesulphadiethylamide (Urelim). Il se montra efficace et bien toléré aux doses de 500 mg. à 2 g. par jour. La somnolence fut le seul effet secondaire observé chez un malade qui en prit un gramme en une dose. Deux malades qui accusaient des effets secondaires avec le probénécide prenaient de l'Urelim en doses efficaces sans difficulté. Urelim semble être utile dans le traitement d'intervalle de la goutte. De même que les autres agents uricosuriques, l'Urelim peut provoquer des attaques aigus de goutte au début du traitement et il faut administrer de la colchicine pendant les premières 6 semaines du traitement. On a comparé l'Urelim aux autres médicaments uricosuriques et les effets de l'Urelim associé à ces médicaments sont à l'étude.

Un neuvo agente uricosúrico en el tratamiento de la gota: p-carboxibenzenosulfadietilamida (Urelim)

Sumario

En seis enfermos con gota se estudió el efecto de un agente uricosùrico nuevo, p-carboxibenzenosulfadietilamida (Urelim). Se mostró eficaz y bien tolerado en dosis diaria de 500 mg. á 2 g. El ùnico efecto secundario fué somnolencia observada en un enfermo que tomó un gramo a la vez. Dos enfermos que acusaron efectos secundarios con probenecid, tomaron dosis eficaces de Urelim sin dificultad. Urelim parece ser ùtil en el tratamiento de intervalo de la gota. Como los demás agentes uricosùricos, el Urelim puede provocar ataques agudos de gota al principio del tratamineto y se debe administrar colchicina durante las seis primeras semanas de tratamiento. So compara el Urelim a otros productos uricosùricos y se estudian los efectos del Urelim asociado a ellos.

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MORNING STIFFNESS IN RHEUMATOID ARTHRITIS*

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Morning stiffness is a common complaint in rheumatoid arthritis. It varies from a scarcely perceptible stiffening of the fingers, sometimes the earliest premonition of disease, to the torpid, turgid immobility which in advanced arthritis is the waking despair of the unhappy patient. The symptom is not specific, occurring also in other forms of arthritis including osteo-arthritis, but it is sufficiently characteristic to head the diagnostic criteria for rheumatoid arthritis proposed by the American Rheumatism Association (Ropes, 1959).

While in severe cases the whole body is involved, it is the hands which are mainly affected. Little attention has been paid to the assessment of objective morning stiffness, and its cause is unknown. A diurnal variation of grip strength in both rheumatoid and normal individuals has been noted by several observers (Bywaters, 1940; Bechtol, 1954; Wright, 1959), who have pointed out the importance of testing grip strength at a constant hour of the day when assessing progress; this variation has been found to diminish during treatment with corticotrophin. Grip testing, while no doubt expressing to some extent the subjective symptom of morning stiffness, is also of course a measure of muscle power unrelated to this symptom, and impaired morning grip strength found in normal subjects must be considered in terms of weakness as well as of stiffness. In rheumatoid patients grip strength is also limited by pain and supervening psychological factors. It therefore seemed desirable to attempt to measure the passive stiffness of a joint, though it is appreciated that this will be affected by the state of extra-articular structures and muscle tone. Moreover, the hands of patients with rheumatoid arthritis sometimes appear more swollen in the early morning than at other times, and the possibility presents itself that this tissue swelling is the cause of morning stiffness.

This paper describes a study of patients with rheumatoid arthritis and morning stiffness and of non-arthritic control subjects, in whom objective measurements were made of joint stiffness and hand volume, as well as of grip strength.

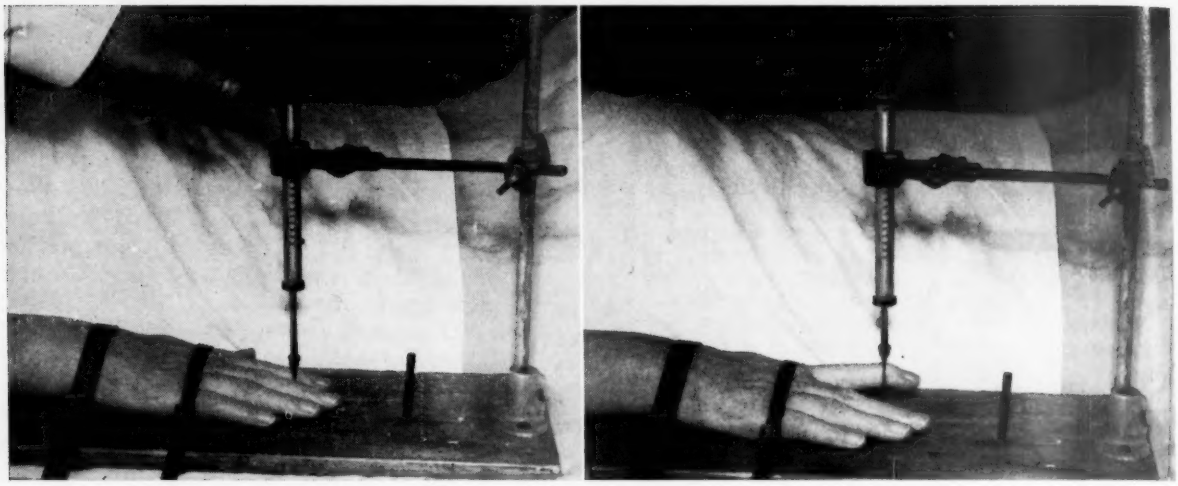
Methods

Passive stiffness of one or other second metacarpophalangeal joint was estimated by elevation of the relaxed finger from the neutral position by an extension spring. The spring was held by a clamp in a vertical position over a wooden platform. The upper end was fixed and the position of the lower end was indicated by a pointer which moved along a vertical scale. Attached to the lower end was a short horizontal bar lying 4·25 cm. above the platform, which would come to rest on the platform when the spring was extended by this distance (Fig. 1, overleaf).

The patient's hand and forearm were strapped to the platform, the hand being secured by a strap which was placed across the metacarpal heads and drawn to the same tightness at each measurement. The hand was placed in such a position that the skin crease opposite the distal interphalangeal joint lay on the horizontal bar of the extended spring. The patient was told to relax the hand completely (easily accomplished after a short demonstration) and the spring was then released, lifting the finger (Fig. 2, overleaf).

The force required to extend the spring was 40 G./cm. Since the spring was extended 4·25 cm. before release, the initial force acting on the relaxed finger was 170 G. As the finger was raised by the spring so the force diminished, the final force

* Presented at a meeting of the Heberden Society, July 2, 1960



Figs 1 and 2.—Measurement of finger displacement, showing position of finger before and after releasing spring.

depending on the position in which the finger came to rest. In practice the distance through which the most supple finger was elevated was never more than 2·5 cm., at which point there was still a force of 70 G. Joint stiffness has been expressed simply in terms of the distance through which the finger was displaced, an adequate expression for the comparative purposes of this study.

Multiple readings undertaken within a short period to test the reproducibility of the method were unacceptable because it was soon clear that repeated extension of the joint not unnaturally decreased its stiffness. Fig. 3 shows fifty successive readings in a normal subject during an afternoon session of an hour and a half, during which time finger displacement is seen gradually to increase; this situation is perhaps analogous to the rheumatoid patient working off his stiffness, or the pianist increasing the suppleness of his fingers by repeatedly clenching and unclenching the hands.

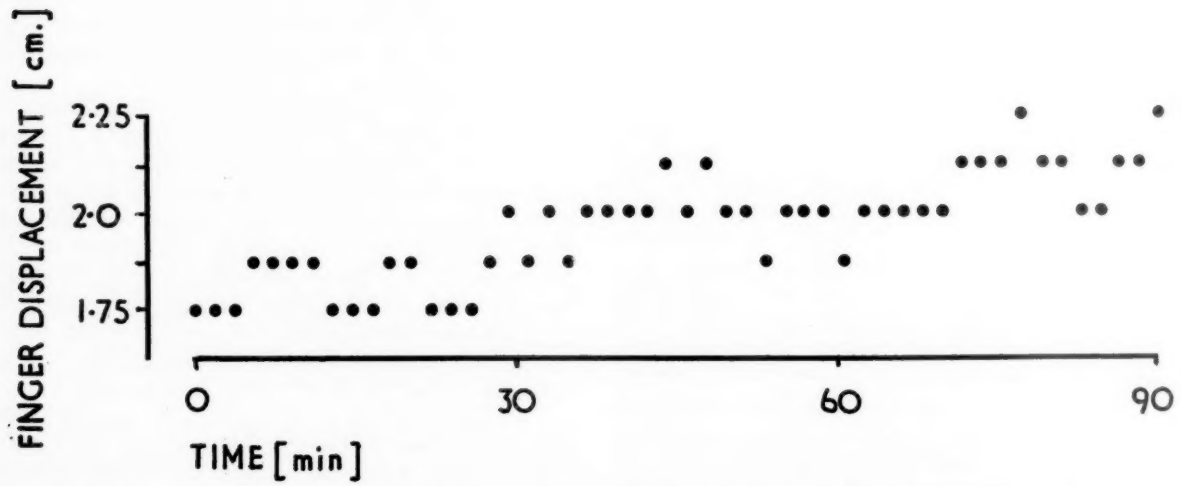


Fig. 3.—Fifty successive estimations of finger displacement in a normal subject in a period of 90 minutes, showing gradual increase in displacement.

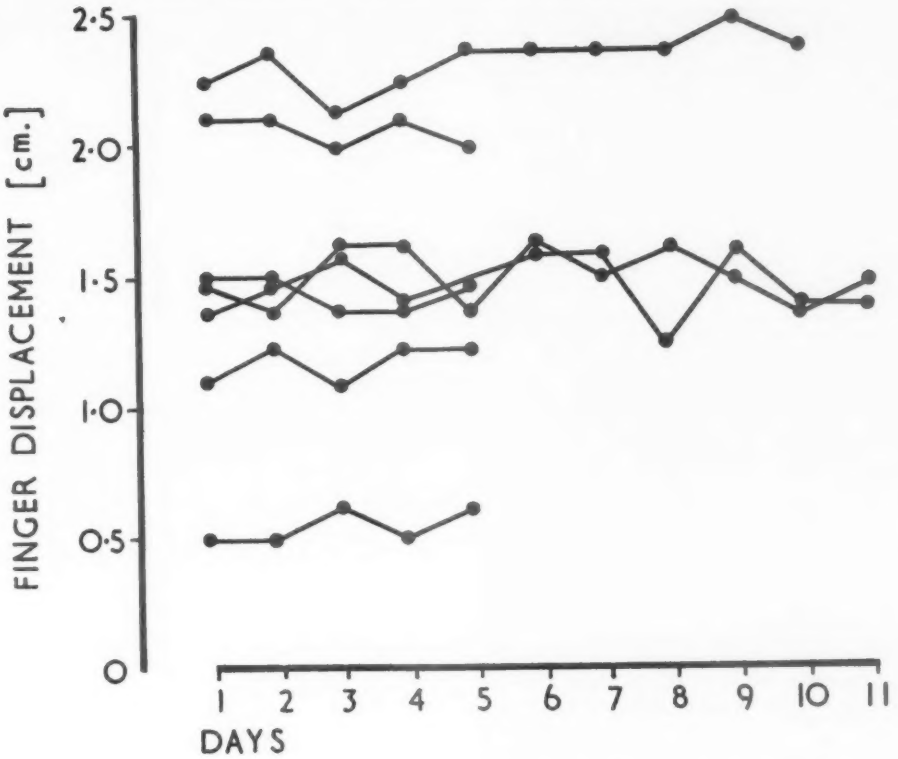


Fig. 4.—Daily measurements of finger displacement on one hand in seven normal subjects.

Fig. 4, however, shows readings (on one hand) of seven normal subjects during periods of from 5 to 11 days at the same time of day. Variability in individual subjects is not excessive, though there are marked differences in finger displacement among this group of people.

To measure hand volume a perspex tank was filled with water at body temperature to the level of an overflow pipe (Fig. 5, overleaf). The hand was immersed to an ink line drawn round the wrist at the level of the ulnar and radial styloid processes and the volume of displaced water was measured. As a test of the accuracy and reproducibility of this method, fifty consecutive readings were taken on a normal subject during a period of 2 hours in the middle of the day. The coefficient of variation was 0·63 per cent. (mean 411·4 ml.; standard deviation 2·6 ml.). In the study the mean of three readings was taken as the hand volume.

Strength of grip was tested with a standardized rubber bag cased in silk attached to a mercury sphygmomanometer, filled with air to an initial pressure of 20 mm. Hg. A mean of three readings was taken. In normal subjects, in whom grip strength exceeded 300 mm. Hg, the bag was attached to an aneroid spring meter.

Morning and evening measurements by these three methods were made in five adult in-patients (four females and one male) who had chronic, active rheumatoid arthritis with a positive sheep cell agglutination test. All complained of subjective morning stiffness.

Measurements were also made in four non-arthritic adult control subjects (three females and one male) with no morning stiffness.

The subjects were tested for between 10 and 20 days as nearly consecutive as possible. The morning measurements were taken soon after waking and before the patient rose from bed: this was usually between 6 and 6.30 a.m. and always before 7 a.m. The evening readings were made in the late afternoon or early evening, usually about 6 p.m. Additional readings were made on several patients at intervals throughout the day.

Fig. 5.—Measurement of hand volume.

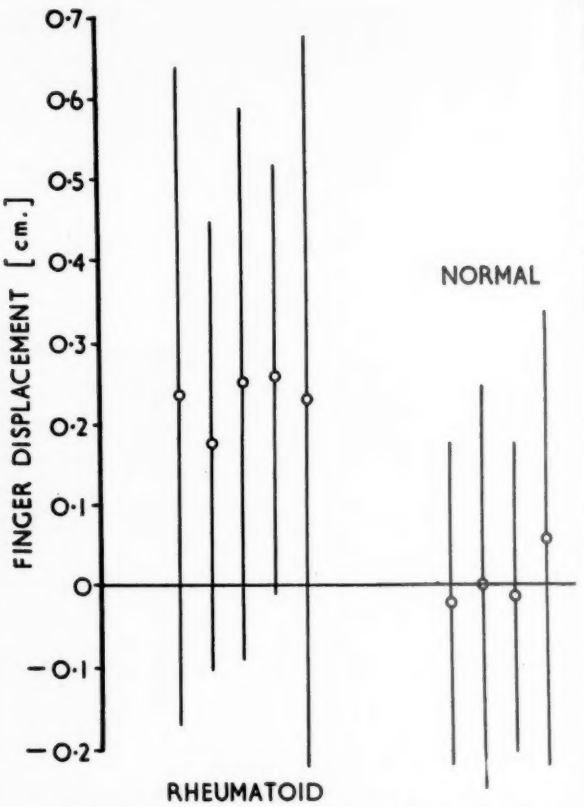


Fig. 6.—Distance by which evening finger displacement exceeded morning displacement in rheumatoid and normal subjects. Circles indicate mean differences, vertical lines two standard deviations above and below the mean.

Results

Morning stiffness in the rheumatoid arthritis patients was usually demonstrable by decreased finger displacement in the morning compared with the evening. The ordinate in Fig. 6 indicates the distance by which evening displacement exceeded morning displacement. In the rheumatoid subjects the finger was elevated on an average between 0·175 and 0·256 cm. further in the evening than in the morning, though as might be expected there was considerable variation shown by the large standard deviation. In the normal subjects the mean difference between morning and evening displacement was close to zero.

The difference between morning and evening hand volumes is similarly shown in Fig. 7 (opposite). In the rheumatoid patients the morning volume usually exceeded that of the evening, the mean differences in the five patients ranging from 6·5 to 17·5 ml. There was again a large variation from day to day. The normal subjects, however, also showed a greater volume in the morning, the mean differences ranging from 5·5 to 7·5 ml.

Evening grip strength usually exceeded that of the morning in both rheumatoid and normal subjects. These findings accord with the previous work mentioned, but Fig. 8 (opposite) shows the variability of the diurnal difference, particularly it seems in normal subjects; it should be pointed out, however, that the absolute grip strength in the rheumatoid patients was less than 200 mm. Hg, whereas in the normal subjects it lay mostly between 300 and 600 mm. Hg, so that relative to the actual grip strength the variability in the two groups is not so dissimilar as this graph suggests.

Most of the change in finger displacement, hand volume, and grip strength took place in the first few hours after waking, coinciding with the disappearance

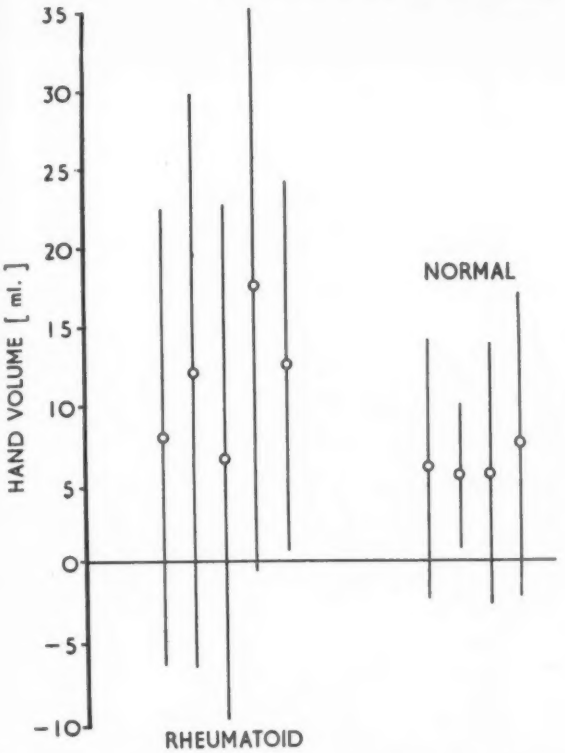


Fig. 7.—Amount by which morning hand volume exceeded evening hand volume in rheumatoid and normal subjects.

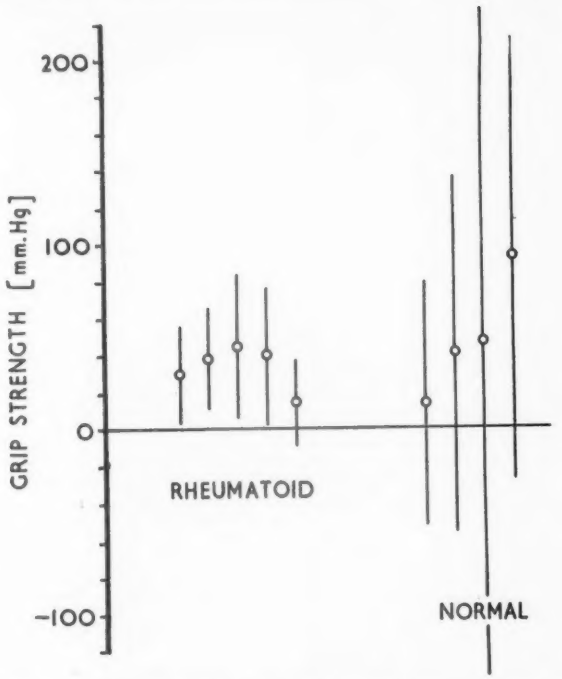


Fig. 8.—Amount by which evening grip strength exceeded morning grip strength in rheumatoid and normal subjects.

of subjective morning stiffness. Fig. 9 (overleaf) shows hourly changes during a day in a patient with rheumatoid arthritis.

All these observations were made while the patients with rheumatoid arthritis were receiving treatment with salicylates. The opportunity was taken in three patients, one of whom is illustrated in Fig. 10 (overleaf), to observe the effect of corticosteroid therapy. Corticosteroids produced an improvement in subjective stiffness, an increase in grip strength and finger displacement, and a decrease in hand volume, together with a reduction in the diurnal variation in all of them. The effects in this case occurred soon after oral prednisolone, 20 mg. daily in four divided doses, was started. The drug was discontinued after 6 days and there was a subsequent return to the pre-treatment state though some improvement in grip strength was maintained. Prednisolone was again started, this time in a dosage of 5 mg. each night only, and a repetition of the effect was seen, though it later became necessary to increase the dose to 5 mg. twice daily, on which the patient has remained very well.

Discussion

Pain and stiffness are two symptoms not always easily distinguishable from each other, since the range of movement in a painful joint is impaired by voluntary or involuntary muscle action. In these investigations, however, finger displacement was never sufficient to be painful in the subjects tested, so that the observed differences between morning and evening displacement could hardly be due to a diurnal variation in the pain sensitivity of articular structures, though the existence of such a variation remains an interesting possibility. Grip strength, on the other hand, is certainly influenced by pain in rheumatoid patients.

The demonstration of objective morning stiffness together with an increase in morning hand volume suggests that the stiffness may be due to an increase in inflammatory oedema in the early morning, perhaps related to a diurnal variation in adrenal corticosteroid production (Perkoff, Eik-Nes, Nugent, Fred, Nimer, Rush, Samuels, and Tyler, 1959). This concept is supported by the diminution or abolition of such variation when corticosteroid treatment is given. It was, however, seen that normal subjects also had a greater hand volume in the morning than in the evening, the difference being as great as in some, but not all, of the rheumatoid arthritis

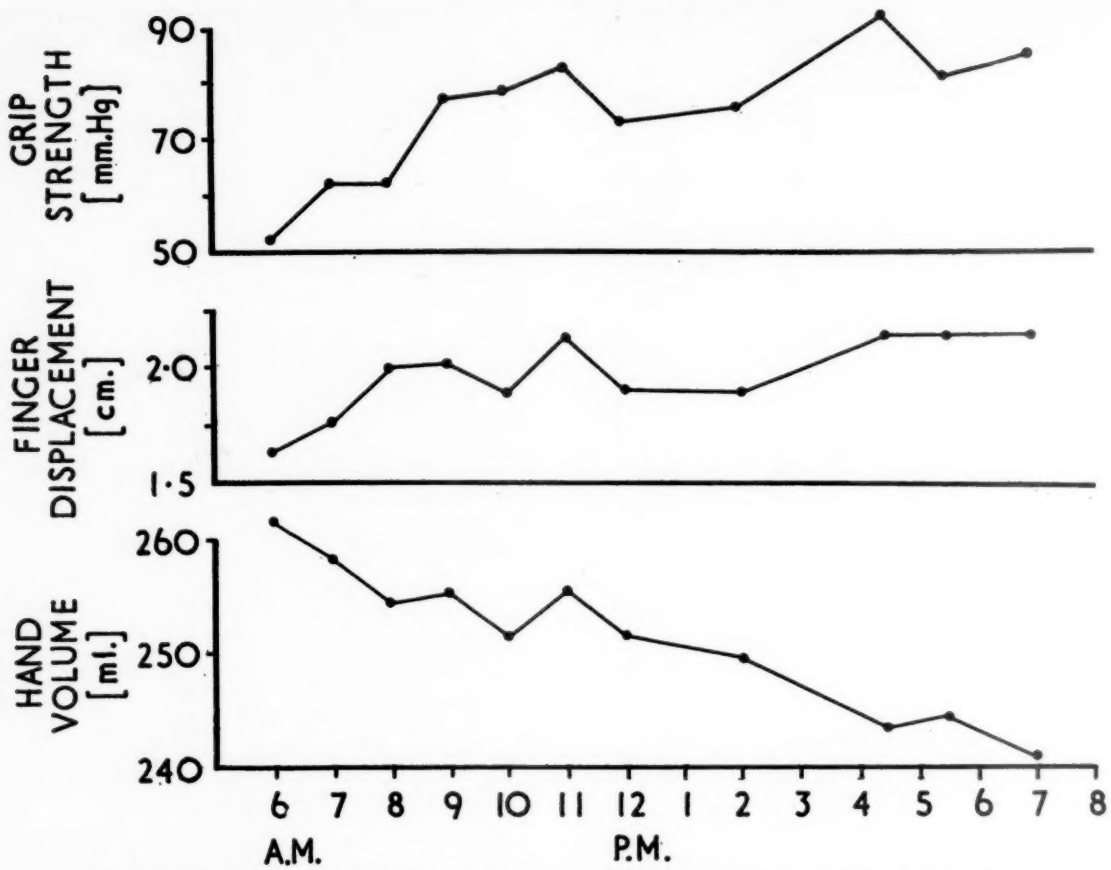


Fig. 9.—Hourly changes in grip strength, finger displacement, and hand volume in a patient with rheumatoid arthritis.

patients. None of the normal subjects complained of morning stiffness, nor did they show any diurnal variation in finger displacement, from which it follows that an increase in hand volume cannot be the entire cause of morning stiffness, though this may be a contributory factor and indeed must be so when gross. It is further conceivable that local periarticular oedema could cause morning joint stiffness with little increase in total hand volume beyond that found in normal subjects. Nevertheless, there probably exists a further mechanism underlying rheumatoid morning stiffness, such as perhaps a diurnal variation in the elasticity of connective tissue.

The morning increase in hand volume seen in normal subjects is probably largely attributable to the local factor of immobility during sleep and to the diminished venous return which is due to lack of muscular pumping action. A further general factor may be involved: there is a diurnal rhythm in the excretion of water and electrolytes, the output being greater by day than by night (Borst and de Vries, 1950; Stanbury and Thomson, 1951). This implies nocturnal tissue fluid retention, of which increased morning hand volume may be a manifestation.

Summary

The subjective complaint of morning stiffness in patients with rheumatoid arthritis has been demonstrated by a matutinal increase in objective joint stiffness and hand volume, and a decrease in grip strength. A similar variation in hand volume and grip strength, but not in joint stiffness, is seen in normal subjects, and it is evident that increased total hand volume is not the entire cause of morning stiffness.

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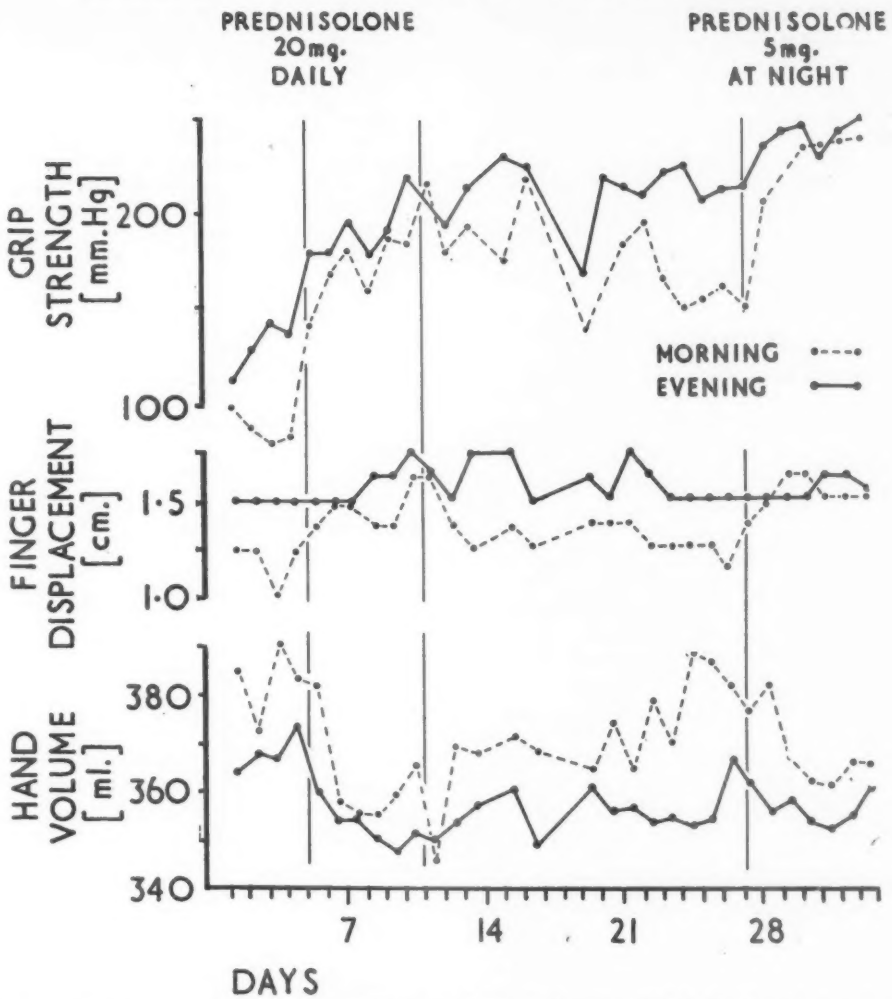

Fig. 10.—Daily measurements of morning and evening grip strength, finger displacement, and hand volume in a patient with rheumatoid arthritis, showing the effect of treatment with prednisolone.

Discussion.—DR. O. SAVAGE (*London*) commented that morning stiffness was one factor in the complicated empirical formulae that had been designed to diagnose and assess rheumatoid arthritis. Until now it had not been possible to measure it accurately and objective methods of assessment were welcome.

PROF. E. G. L. BYWATERS (*London*) said that 20 years before he had found, on measuring the diurnal variation of grips and of finger-joint circumference in normal and rheumatoid subjects, that there was much individual variation in both categories in regard to grip and swelling: some showed large diurnal variation, others none. The circumference of the finger between joints showed similar variations. There appeared to be a relationship between finger swelling and grip variation, especially as shown by immobilization, and it seemed possible that swelling of the fingers might not be shown by measurements of whole hand volume.

DR. V. WRIGHT (*Leeds*) asked Dr. Scott whether he had allowed for variation in finger length in his measurements of joint stiffness, since he would be aware that the force exerted was a product of the tension in the spring and the length of the finger. What was the standard deviation of measurements with the hand left in the apparatus, and with it removed between readings? This was of great importance if conclusions were to be drawn about changes related to morning stiffness.

DR. SCOTT replied that no account had been taken of finger length because comparisons of joint stiffness were made only in respect of the same patient in the morning and the evening. There was a great deal of variation in objective stiffness among normal and rheumatoid subjects, with a considerable overlap between the two groups. The hand had been removed from the apparatus between measurements when multiple readings were undertaken to test the reproducibility of the method, but stiffness had been found to diminish with repeated extension of the joint.

In a reply to a question from Prof. Bywaters, he said that no patients had been investigated under anaesthesia.

Enraidissement matinal dans l'arthrite rhumatismale

RÉSUMÉ

Le symptôme d'enraidissement matinal chez des malades atteints d'arthrite rhumatismale fut expliqué par une augmentation matinale de l'enraidissement articulaire objectif et du volume de la main et par une diminution de la force de la poigne. Une variation similaire dans le volume de la main et dans la force de la poigne, mais non pas dans l'enraidissement articulaire, survient chez des sujets normaux; il est donc évident que l'augmentation du volume total de la main n'est pas la seule cause de l'enraidissement matinal.

Rigidez matutina en artritis reumatoide

SUMARIO

El síntoma de rigidez matutina en enfermos con artritis reumatoide fué demostrado por un incremento matutino de la rigidez articular objetiva y del volumen de la mano y por una disminución de la fuerza al asir. Una variación similar en el volumen de la mano y la fuerza al asir, pero no en la rigidez articular, aparece en sujetos normales; es, pués, evidente que el aumento del volumen total de la mano no es la única causa de la rigidez matutina.

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PRODUCTION OF ARTHRITIS IN THE RABBIT BY THE LOCAL INJECTION OF THE MUCOPOLYSACCHARIDE CARAGHEENIN

BY

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In the laboratory study of rheumatoid arthritis the need has long been felt for a convenient animal replica of this disease. Very many techniques have been used during the past century for this purpose; they have recently been reviewed (Gardner, 1960). Forms of experimental arthritis have been studied in the monkey, horse, sheep, goat, pig, dog, rabbit, guinea-pig, rat, mouse, and chick-embryo, but none has provided a universally acceptable model. In the hope that an easily reproducible form of laboratory arthritis might lead to an advance in our understanding of the pathogenesis of rheumatoid arthritis, experiments have been made with the sulphated mucopolysaccharide caragheenin. This substance, obtained from the Irish moss *Chondrus crispus*, or from Scottish seaweed, has previously been used in the study of collagen fibre formation because of its remarkable capacity to stimulate local inflammation dominated by intense macrophage aggregation and by fibroblastic proliferation (Jackson, 1956a, b; Williams, 1957).

In the experimental study of arthritis, caragheenin appears to offer certain advantages as a stimulating material. Owing to its chemical structure, its position in the injected tissues is readily determined by the periodic acid-Schiff reaction. It is easily dissolved in isotonic saline, forming a gel at room temperature but becoming less viscous on warming. Sterilization can be effected by boiling without impairing the capacity of the material to cause inflammation, while the presence of sulphate groups on the molecule suggests that future studies with labelled caragheenin may be possible.

Material

A supply of a crude extract of caragheenin was obtained through the courtesy of the director of the Seaweed Research Station at Musselburgh. Partial purification of the crude extract by dialysis did not alter the inflammatory reaction produced on injection. For use, the caragheenin powder was made up in isotonic normal saline and sterilized by boiling.

English rabbits of both sexes were used; the animals were mature and of good nutritional status, and were maintained on a diet containing all known essential factors.

Guinea-pigs were of a laboratory-bred strain. They were large, mature, and well-fed. Their diet contained all known essential nutritional factors.

For comparison with animal material, joints from twenty cases of rheumatoid arthritis were selected. These cases formed part of a series in which a *post mortem* examination had been conducted personally.

Methods

The injection of caragheenin was undertaken in three ways:

(1) Intradermally, as a dilute solution, without anaesthesia, into the skin of guinea-pigs.
(2) Under ether anaesthesia, into the joints of guinea-pigs.
(3) Under pentobarbitone anaesthesia, into the joints of rabbits.

Material for biopsy was collected under ether anaesthesia. Animals were killed by the injection of pentobarbitone.

Tissue samples were placed in neutral formol saline immediately after biopsy or death. Bone was decalcified in a formic acid—sodium citrate mixture. Paraffin-embedded sections were cut at 4-8 μ, and were stained with haematoxylin and eosin, by the periodic acid-Schiff reaction, and by Masson's trichrome method.

Procedure

The experiment was conducted in three parts:

(1) The optimal strength of a solution of caragheenin required to give a readily detectable inflammatory re-

sponse was determined by a series of injections into guinea-pig skin.

0·1 ml. of each of the following concentrations of the caragheenin solution were injected into the shaved dorsal skin of a guinea-pig: 0·25, 0·5, 1, and 2 per cent. A biopsy of each lesion was performed 36 hours later.

(2) A general assessment of the type of reaction to be expected following intra-articular injection, and the size and frequency of injections required to give a brisk articular response, were determined by the injection of amounts of the solution of optimal concentration into the joints of eight guinea-pigs.

Single injections of 0·1 ml. of a 1 per cent. solution of caragheenin were made into the large limb joints of guinea-pigs at the following intervals before biopsy: 1 month, 2 weeks, 1 week, 3 days, 1 day, and 6 hours.
Repeated injections of 0·1 ml. of the 1 per cent. solution were made at the following intervals:

(*i*) Eleven injections at 3-day intervals
(*ii*) Six injections at 7-day intervals
(*iii*) Four injections at 7-day intervals
(*iv*) Four injections at 14-day intervals
(*v*) Three injections at 14-day intervals
(*vi*) Three injections at 21-day intervals

(3) A more detailed study was made of the articular response to the injection at optimal intervals of moderate to large amounts of the solution of optimal strength, using for this purpose eleven rabbits.

The amounts of caragheenin injected into the principal limb joints at stated intervals are shown in the Table.

After these series of injections were completed, the animals were killed and the tissues examined histologically.

Results

(1) Response of Guinea-pig Skin.—An optimal response was given by the injection of 0·1 ml. of the 1 per cent. solution. An intense histiocytic reaction, with smaller numbers of polymorphonuclear leucocytes, was concentrated within the deeper layers of the dermis and the subcutaneous tissues.

(2) Response of Guinea-pig Joints.—After 6 hours a single injection of 0·1 ml. of the 1 per cent. solution produced an intense polymorphonuclear leucocytic inflammatory cell reaction. After 24 hours and after 3 days the cellular characteristics of the inflammatory infiltrate changed to include a progressively larger proportion of histiocytes and later fibroblasts. After 1 month no detectable abnormality remained.

Intra-articular injection of 0·1 per cent. and of 0·5 per cent. solutions produced slight responses only. A greatly exaggerated reaction was detected after the 1 per cent. solution and this strength was accepted as optimal. The viscosity of the 2 per cent. solution, which produced only a little more

TABLE

ARTICULAR RESPONSE IN TEN RABBITS

Series	Rabbit No.*	Dose (ml.)	Frequency (per week)	Duration (wks)	No. of Injections
Experimental	1 2	0·5 ml. of 1 per cent. solution rising to 1 ml. of 1 per cent. solution	Once	6 10	7 11
	3 4 5	1 ml. of 1 per cent. solution	Twice	3 3 3	6 6 6
	8 9 10	Amounts of 1 per cent. solution increasing from 1 to 5 ml. per joint	Twice	4·5 4 3	9 8 6
Control	6	Increasing amounts intravenously to a total of 19 ml.	Once	11	11
	7	0·5-1 ml. normal saline intra-articularly	Once	10	10

* Rabbit No. 11 died during the course of the experiment

inflammatory response, became so great that much difficulty was experienced in handling the material before injection, even with prior warming of the mixture and of the syringe.

(3) **Response of Rabbit Joints.**—A certain variability was observed, possibly related to the varying difficulty experienced in injecting the carageenin solution. Generally, to produce a prolonged arthritic response, it was necessary to inject carageenin at intervals of not more than 3 to 7 days; for this purpose the 1 per cent. solution was most convenient. With this procedure examination of the joints after intervals of 6 to 10 weeks revealed inflammatory proliferation of the synovial villi (Figs 1 and 2), with increased cellularity, and a marginal attachment of synovia to the superficial parts of the articular cartilages (Figs 3 and 4). Progressive replacement fibrosis of articular cartilage (Figs 5 and 6) by cellular connective tissue in continuity with that of the hypercellular synovial fringes commonly resulted in the formation of pannus, a change apparently analogous with the marginal "invasion" of articular cartilage seen in rheumatoid arthritis. The cellular reaction differed from that seen in rheumatoid arthritis, however, in that the predominant cell type present was the lymphocyte and not the plasma cell (Figs 7 and 8). Nevertheless, the infiltrate was sometimes perivascular in distribution (Figs 9 and 10) and was accompanied by periarticular fibrosis (Figs 11 and 12). In the superficial margins of occasional hyperplastic synovial villi were accumulations of material staining positively for fibrin (Figs 13 and 14), but fibrinoid change was not an invariable characteristic of the reaction. Osteoclastic bone reabsorption was an occasional finding (Figs 15 and 16).

When a comparison was made between the animal joints and those from patients dying with rheumatoid arthritis, it proved possible, by the exercise of considerable selection, to find areas in both animal and human tissue which were morphologically very similar. Since the histological characteristics of the joints in rheumatoid arthritis are not individually specific, there was no justification for deducing that the rabbit arthritis produced by carageenin offered more than a crude replica of the human disease. Nevertheless, it was felt that the model offered certain practical advantages which might make it acceptable as a basis for future use, and in particular for the laboratory study of iron metabolism in animals with a chronic arthritis (Richmond, Gardner, Roy, and Duthie, 1956; Richmond, Roy, Gardner, Alexander, and Duthie, 1958.

Fig. 1.—Rabbit 1, seven injections at weekly intervals. Widespread lymphocytic reaction in hyperplastic synovial villi. Haematoxylin and eosin × 60.

Fig. 2.—For comparison with Fig. 1. Synovial villi from an interphalangeal joint in a case of long-standing rheumatoid arthritis. Haematoxylin and eosin × 140.

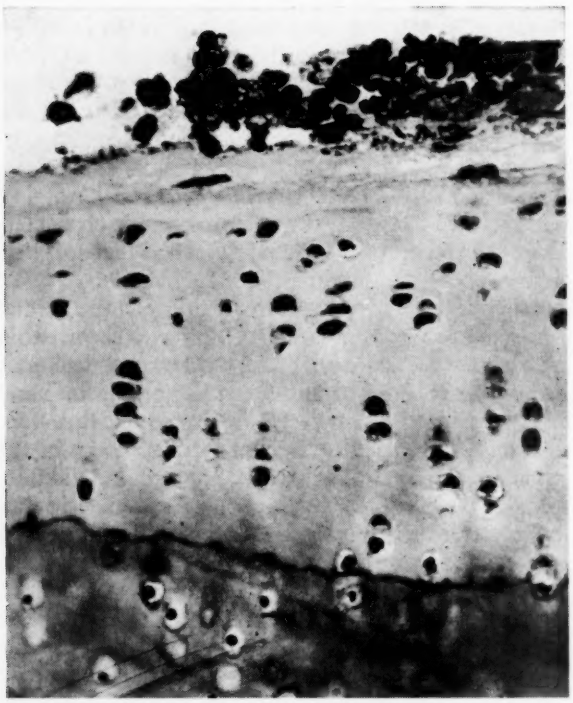

Fig. 3.—Rabbit 2, seven injections at weekly intervals. Mononuclear cells, fibroblasts, and cell debris form an irregular pannus in continuity with the superficial layer of articular cartilage.
Haematoxylin and eosin × 350.

Fig. 4.—For comparison with Fig. 3. Marginal replacement fibrosis of articular cartilage from an interphalangeal joint in a case of long-standing rheumatoid arthritis.
Haematoxylin and eosin × 350.

Fig. 5.—Rabbit 5, injections twice weekly for 3 weeks. Margin of articular cartilage undergoing replacement by lymphocytes and histiocytes.
Haematoxylin and eosin × 200.

Fig. 6.—For comparison with Fig. 5. Replacement of border of articular catilage of finger joint in a case of old active rheumatoid arthritis.
Haematoxylin and eosin × 200.

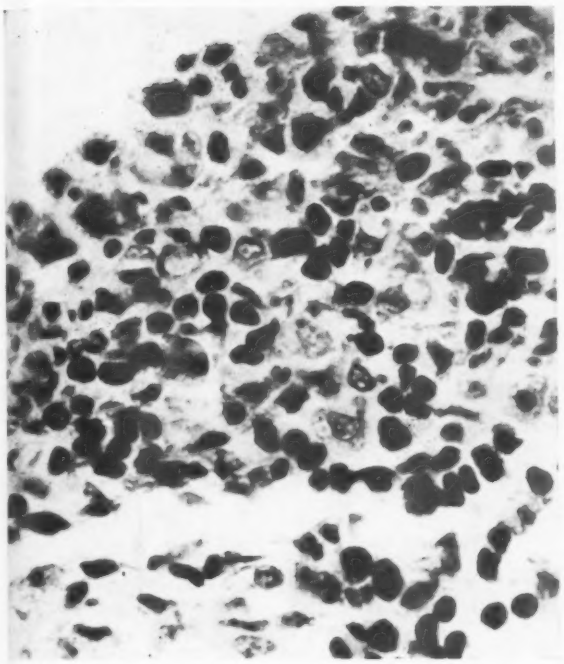

Fig. 7.—The cellular response in arthritis induced by carageenin is predominantly histiocytic.
Haematoxylin and eosin × 640.

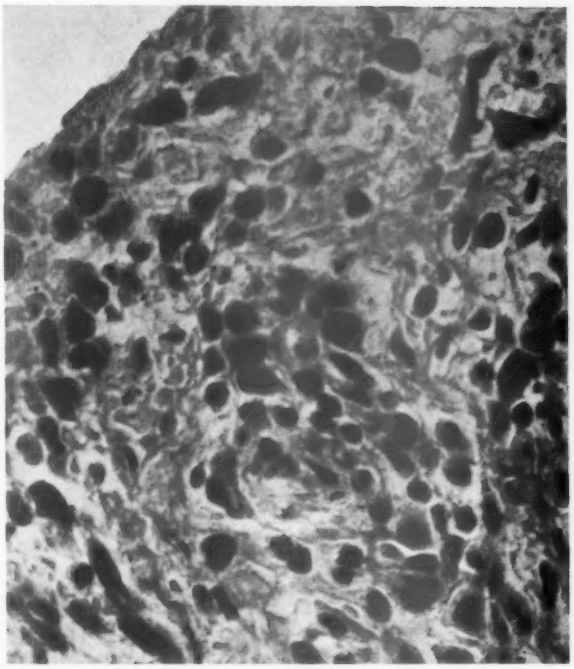

Fig. 8.—In contrast with Fig. 7. The predominance of plasma cells is pathognomonic of active rheumatoid arthritis.
Haematoxylin and eosin × 650.

Fig. 9.—Rabbit 5, six twice-weekly injections. Both in carageenin arthritis and in rheumatoid arthritis there is a tendency for the aggregation of inflammatory cells to become perivascular.
Haematoxylin and eosin × 95.

Fig. 10.—For comparison with Fig. 9. Perivascular fibrosis and inflammatory cells at margin of interphalangeal joint in active rheumatoid arthritis.
Haematoxylin and eosin × 100.

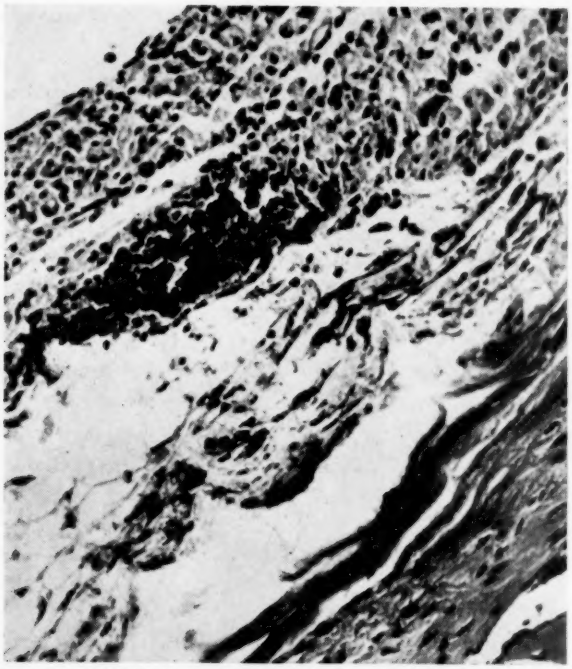

Fig. 11.—Rabbit 5. Lymphocytic foci within the para-articular soft tissues.
Haematoxylin and eosin × 200.

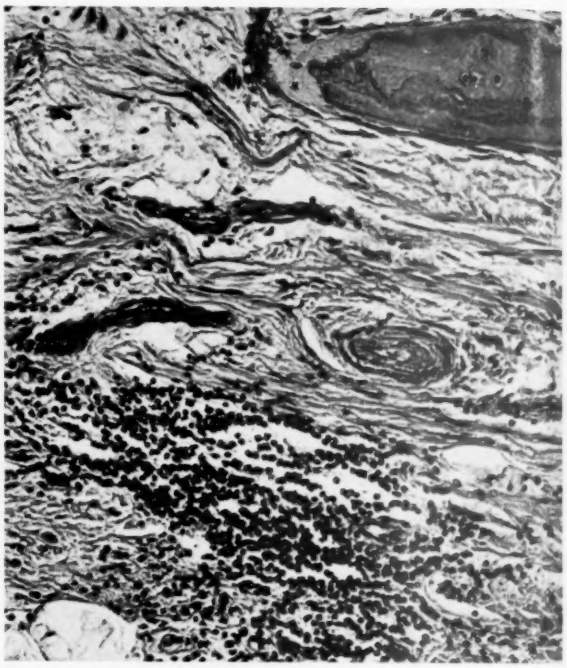

Fig. 12.—Comparable lymphocytic foci are frequently seen in the soft tissues bounding involved metacarpophalangeal joints in rheumatoid arthritis.
Haematoxylin and eosin × 200.

Fig. 13.—Rabbit 7, left fore-limb. Fibrin deposited superficially on hyperplastic cellular synovial tissue.
Haematoxylin and eosin × 95.

Fig. 14.—For comparison with Fig. 13. Fibrinoid in margin of synovial villus in metacarpophalangeal joint in a case of active long-standing rheumatoid arthritis.
Haematoxylin and eosin × 200.

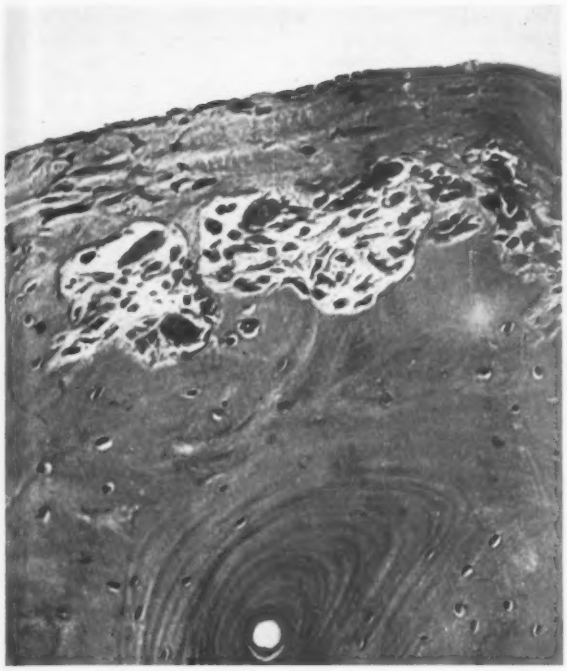

Fig. 15.—Rabbit 6. Osteoclastic bone reabsorption is frequent at the margins of involved joints in arthritis caused by carageenin. Haematoxylin and eosin × 200.

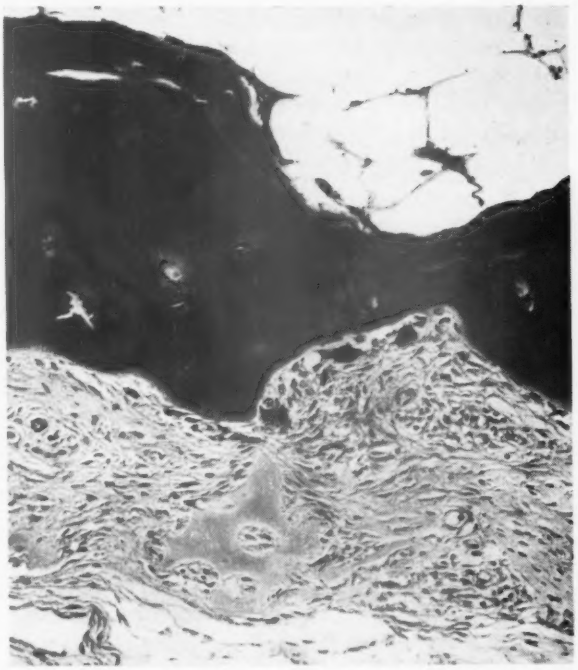

Fig. 16.—For comparison with Fig. 15. Similar appearances are found in active chronic rheumatoid arthritis. Haematoxylin and eosin × 200.

Discussion

The experiment described in the present paper has shown that the large limb joints of guinea-pigs and of rabbits respond to the injection of a sterile solution of the mucopolysaccharide carageenin in isotonic saline by the production of an inflammatory response, which can be perpetuated by repetitive injection, and which results after 6 to 10 weeks in the appearance of histological changes which individually may resemble closely those found in rheumatoid arthritis in the human. Very many alternative methods for the production of arthritis in laboratory animals have previously been described, but the present method is both simple, reproducible, and free from some of the uncontrolled incidental factors which have plagued so many of the methods described in the literature. Carageenin is more readily obtained, more easily handled, and less disturbed by environmental changes than the mucopolysaccharides used by Jones and Carter (1954), Jones, Carter, and Rankin (1954), Jones and Carter (1957a, b), and Jones and Mayne (1958). Its reactivity appears to depend entirely upon a local stimulus to inflammation, and it is not known to be antigenic. Repeated injections maintain but do not exaggerate local responses, and repeated systemic administration has caused no detectable change in the lungs, liver, and other viscera.

Whether future experiments will show that it is possible to reproduce in animals an arthritis comparable in every way to rheumatoid arthritis in the human is uncertain. It appears from the large amount of work performed on small rodents that these species are not likely to yield the answer to this question. The present author is among those who believe that it may prove necessary to turn to the primates before a complete animal replica of the human disease is found; this approach to the problem will be both arduous and costly.

Summary

(1) The highly sulphated mucopolysaccharide carageenin extracted from Irish moss or from Scottish seaweed has been used to induce an articular inflammatory reaction in guinea-pigs and in rabbits. Experiment has shown that an optimal response is obtained when a 1 per cent. solution in sterile isotonic saline is injected at intervals of not more than 7 days for at least 6 weeks.

(2) Under these circumstances an arthritis may be produced the individual histological characteristics of which may closely resemble those of selected

cases of rheumatoid arthritis in the human. No claim can legitimately be made to have reproduced any particular form of human arthritis, but the procedure offers certain advantages for the future study of experimental arthritis.

The constant advice and encouragement of Dr. J. J. R. Duthie are gratefully acknowledged.

During the period in which this work was undertaken the Rheumatic Research Unit was in receipt of grants from the Nuffield Foundation, from the Medical Research Council, and from Boots Pure Drug Company.

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Production d'arthrite chez le lapin par injection locale de mucopolysaccharide *caragheenin*

RÉSUMÉ

(1) Le mucopolysaccharide très sulfaté *caragheenin*, extrait de l'algue marine irlandaise ou écossaise (*Irish moss* ou *Scottish seaweed*) fut employé pour induire une réaction inflammatoire articulaire chez des cobayes et des lapins. On détermina expérimentalement qu'une réponse optimum s'obtient lorsqu'on injecte à des intervalles de 3 à 7 hours, pendant au moins 6 semaines, une solution à 1 pour cent en l'eau physiologique stérile.

(2) En ces circonstances on peut produire une arthrite dont les traits histologiques individuels ressemblent de près ceux des cas selectionnés d'arthrite rhumatismale humaine. On ne peut pas prétendre légitimément qu'on ait reproduit une forme particulière d'arthrite humaine, mais le procédé offre certains avantages pour l'étude future de l'arthrite expérimentale.

Producción de artritis en el conejo por inyección local de mucopolisacarido *caragheenin*

SUMARIO

(1) El altamente sulfatado mucopolisacarido *caragheenin* extraido del alga marina irlandesa o escocesa (*Irish moss* o *Scottish seaweed*) fué usado para inducir una reacción inflamatoria articular en cobayos y conejos. Experimentalmente se determinó que la respuesta óptima se presenta cuando se inyecta con intervalos no superiores a 3-7 días por no menos de 6 semanas una solución al 1 por ciento en suero salino isotónico esteril.

(2) En estas circunstancias puede ser producida una artritis de características histológicas individuales con una semejanza cercana a casos seleccionados de artritis reumatoide en el hombre. No es posible afirmar que se haya reproducido una forma particular de artritis humana, pero el procedimiento ofrece ciertas ventajas para el futuro estudio de la artritis experimental.

Ann. rheum. Dis. (1960), **19**, 377.

LIGUE INTERNATIONALE CONTRE LE RHUMATISME

REPORT OF THE COMMITTEE ON NOMENCLATURE AND CLASSIFICATION

Submitted to and approved by the Ligue at the IV International Congress, Toronto, 1957

We herewith submit the nomenclature and classification recommended by us for adoption.

This committee conducted its discussions by correspondence after the first meeting held in Geneva in 1953, when a tentative nomenclature and classification were considered, subject to further revision by correspondence.

In April, 1954, an Expert Committee on Rheumatic Diseases of the World Health Organization published a classification based on the preliminary nomenclature considered by us at Geneva, when a representative of the Expert Committee attended our first meeting.*

Our next meeting took place at The Hague. The version of the Expert Committee, with minor modifications, was recommended for adoption. The nomenclature then was sent to the different national organizations affiliated with the Ligue. Four national groups and a number of leading rheumatologists, in the Americas and abroad, responded with suggestions, some of which have now been included.

The nomenclature is presented by us in English and Latin. When accepted, the Latin version is to be translated by each national league into its own language for standard use.

* Expert Committee on Rheumatic Diseases (1954). W.H.O. Technical Report Series, No. 78.

The discussions of this committee have shown that a perfect nomenclature, acceptable to all without points of difference, can hardly be achieved. A practical, realistic approach to this problem, beset as it is by the difficulties of traditional and national usages, will require compromise until a classification likely to be universally accepted and applied can be achieved. We can only hope that our efforts will prove to be a helpful start toward that goal.

This committee recommends that the nomenclature committee shall continue to function in order to revise terminology and to evaluate periodically the addition of new terms as developments occur.

Committee Members:

Pedro Barceló (*Spain*)
Florent Coste (*France*)
Frantisek Lenoch (*Czechoslovakia*)
A. Robecchi (*Italy*)
Anibal Ruiz Moreno (*Argentina*)
Oswald Savage (*England*)
R. Schoen (*Germany*)
Otto Steinbrocker (*U.S.A., Chairman*)
Robert M. Stecher (*U.S.A., ex officio*)
K. M. Walthard (*Switzerland*)

CLASSIFICATION

I. Diseases and Disorders of Connective Tissue commonly accepted as Rheumatic

(A) Articular

(1) *Inflammatory*

Idiopathic

(*a*) Rheumatic fever

(*b*) Rheumatoid arthritis

Atypical Forms:

Arthritis with psoriasis, psoriatic arthropathy

Juvenile rheumatoid arthritis (Still-Chauffard's disease)

I. Morbi et Perturbationes universe Rheumaticae habitae

(A) Affectiones Articulares

(1) *Affectiones Inflammatoriae*

Idiopathicae

(*a*) Febris rheumatica

(*b*) Polyarthritis chronica progressiva

Formae atypicae:

Arthritis psoriatica

Polyarthritis progressiva spleno-adenomegalica (morbus Still-Chauffard)

Rheumatoid arthritis with spleno-adenomegaly and leucopenia (Felty's syndrome)
Polyarthritis with kerato-conjunctivitis sicca (Sjögren's syndrome)
Polyarthritis with nonspecific urethritis (Reiter's syndrome)
Special Forms:
Ankylosing spondylitis (spondylarthritis)
Intermittent hydrarthrosis
Palindromic rheumatism

Infective
Arthritis due to specific infection

(2) *Degenerative*
Osteo-arthritis, degenerative joint disease, or osteo-arthrosis
Intervertebral disk lesions

(B) Non-articular
Bursitis
Fasciitis
Fibrositis
Myositis, myalgia
Neuritis, neuropathy, neuralgia
Disorders of fatty tissue, panniculitis
Periarthritis
Tendovaginitis, tenosynovitis
Tendinitis, tendinosis, peritendinitis

II. Diseases and Disorders with Rheumatic Features

(A) Traumatic and Mechanical
Traumatic arthropathy
Postural syndromes

(B) Inflammatory, Idiopathic
Dermatomyositis
Periarteritis nodosa and arteritis
Scleroderma
Systemic lupus erythematosus

(C) Hypersensitivity States with Musculo-articular Reactions to Serum, Drugs, etc.
Erythema multiforme
Erythema nodosum
Purpura (various types)
Purpuric rheumatism
Serum sickness

(D) Metabolic Disturbances
Gout
Alcaptonuria

(E) Endocrine Disturbances
Hyperparathyroidism
Acromegaly
Myxoedema
Osteoporosis, menopausal, senile, etc.

Polyarthritis progressiva spleno-adenomegalica et leucopenica (syndroma Felty)
Polyarthritis cum kerato-conjunctivitis sicca (syndroma Sjögren)
Polyarthritis urethrica simplex (syndroma Reiter)
Formae speciales:
Spondylarthritis ankylopoietica
Hydrops articulorum intermittens
Rheumatismus palindromicus

Infectiosae
Arthritis infectiosa specifica

(2) *Affectiones degenerativae*
Osteoarthrosis deformans aut morbus articulorum degenerativus
Laesiones discorum intervertebralium

(B) Affectiones Extraarticulares
Bursitis
Fasciitis
Fibrositis
Myositis, myalgia
Neuritis, neuropathia, neuralgia
Perturbationes textus adiposi, panniculitis
Periarthritis
Tendovaginitis, tenosynovitis
Tendinitis, tendinosis, peritendinitis

II. Morbi et perturbationes characteres rheumaticos praebentes

(A) Affectiones Traumaticae
Arthropathia traumatica
Syndromata statica

(B) Affectiones Inflammatoriae, Idiopathicae
Dermatomyositis
Periarteritis nodosa
Scleroderma
Lupus erythematosus disseminatus

(C) Status Hypersensibiles cum Reactionibus Musculo-articularibus ad Serum, Medicamina, et cetera
Erythema multiforme
Erythema nodosum
Purpura varia
Purpura rheumatica
Morbus allergicus

(D) Perturbationes Metabolicae
Arthritis urica (seu uratica)
Alcaptonuria

(E) Perturbationes Endocrine
Hyperparathyroidismus
Acromegalia
Myxoedema
Osteoporosis menopausalis, senilis, et ceterae

(F) Blood Diseases
Leukaemia
Haemophilia

(G) Pulmonary Diseases
Sarcoidosis
Hypertrophic pulmonary osteo-arthropathy

(H) Diseases and Disorders of the Nervous System
Neurogenic Arthropathy
Reflex dystrophy

(I) Psychiatric States and Psychological Syndromes

(J) Neoplastic Diseases
Neoplasms of articular and periarticular tissues

(K) Osteochondrodystrophies

(F) Morbi Sanguinis
Leukaemia
Haemophilia

(G) Morbi Pulmonum
Sarcoidosis
Osteopathia hypertrophicans toxica

(H) Morbi et Perturbationes Systematis Nervosi
Arthropathia neurogenica
Dystrophia reflexiva

(I) Status Psychiatrici et Syndromata Psychogenica

(J) Morbi Neoplastici
Neoplasmata textus articularis et periarticularis

(K) Osteochondrodystrophiae

BOOK REVIEW

Calcium Metabolism and the Bone. By Paul Fourman. 1960. Pp. 325, 6 figs, bibl. Blackwell Scientific Publications, Oxford. (37*s.* 6*d.*)

This is a concise and scholarly review of metabolic bone disease from the point of view of the clinician. The text is clear and readable and is brought to life by quotations from case histories of historical interest. Metabolic bone disease can be a confusing subject: renal disease causes hyperparathyroidism and hyperparathyroidism causes renal disease; rickets due to lack of vitamin D causes aminoaciduria and primary renal diseases with aminoaciduria cause rickets; widening of osteoid seams in the bones may result from both lack of, or excess of, vitamin D: one is grateful for Dr. Fourman's expert guidance in this jungle of cause and effect. It is at first surprising, then a pleasure, to realize that the author holds one's attention and makes his points almost entirely without illustrations. Some may find this a drawback.

The three subdivisions of the book, cover, first, aspects of the physiology of bone and calcium metabolism, secondly, the primary disorders of bone and calcium metabolism, and thirdly, the results of renal disease upon bone and its minerals. The methods for commonly-used diagnostic tests are summarized in an appendix. Starting with any one feature, such as nephrocalcinosis or hypercalcaemia, the reader will find a useful list of differential diagnoses to guide him in further investigations. From the point of view of readers of the *Annals of the Rheumatic Diseases*, one chapter, that on the various acute and chronic articular complications of metabolic bone diseases, has yet to be written. However, that is a minor grumble. The most valuable feature of this book will be as a source of references for further reading. There are an enormous number of references (they fill 75 pages, as opposed to 206 pages of text) and the titles of articles quoted are given in full. The book can be warmly recommended. A. St. J. Dixon.

GAIRDNER FOUNDATION

Awards totalling $30,000 for work in arthritis and heart disease have been made during 1960 to four American and two British medical scientists.

United States of America

Dr. John H. Gibbon, Jr., Professor of Surgery and Director of Surgical Research, Jefferson Medical College, Philadelphia, for his use of an artificial heart for the surgical correction of a heart defect in humans.

Dr. William F. Hamilton, Professor of Physiology, University of Georgia School of Medicine, for his work in the use of dyes injected into the blood stream to determine blood flow and distribution in heart disease.

Dr. Karl Meyer, Dean of Medicine, Columbia University, New York, for his contributions to modern concepts of the chemical structure and functions of the so-called binding substance of connective tissue.

Dr. Arnold R. Rich, Baxley Professor Emeritus of Pathology, Johns Hopkins University, Baltimore, for his investigations into the allergic responses to drugs.

Great Britain

Dr. John McMichael, Professor of Medicine, University of London, for his application of the technique of cardiac catheterization.

Dr. Joshua H. Burn, retired Professor of Pharmacology, Oxford University, for contributions to knowledge of the action of drugs in cardiovascular disease.

Ann. rheum. Dis. (1960), **19**, 380.

HEBERDEN SOCIETY

The Heberden Library.—A new catalogue, prepared with the help of Dr. F. L. N. Poynter and Mr. R. J. Durling of the Wellcome Historical Medical Library, lists 278 books devoted to rheumatism, gout, and arthritis, mostly published before 1914. The library is now housed at the Apothecaries Hall, Blackfriars Lane, E.C.4.

Clinical Meeting.—A meeting was held on July 1 and 2, 1960, at the Clinical Sciences Building, Manchester Royal Infirmary. The president, Dr. F. Dudley Hart, was in the chair and presented the first paper: "The Empire Rheumatism Council Clinical Trial of Gold Therapy in Rheumatoid Arthritis".*

A Controlled Trial of Chloroquine Therapy in Polyarthritis.† A. J. POPERT, K. A. E. MEIJERS, J. SHARP, and F. BIER (*Manchester*).

At the invitation of the President, DR. A. FREEDMAN (*London*) reported the results of a trial of chloroquine therapy conducted with DR. V. L. STEINBERG at the London Hospital since 1956.‡

A Study of Morning Stiffness in Rheumatoid Arthritis.§ J. T. SCOTT (*London*).

Analysis of Joint Stiffness. V. WRIGHT and R. J. JOHNS (*Leeds*).†

Familial Aggregation in Generalized Osteo-Arthrosis. J. S. LAWRENCE (*Manchester*): First-degree relatives of persons with osteo-arthrosis in six or more joints discovered in population studies were examined clinically and radiologically and their serum was tested for rheumatoid factor.

An increased prevalence of both generalized osteo-arthrosis and sero-negative inflammatory polyarthritis was found in these relatives. This study suggested the possibility of two main types of generalized osteo-arthrosis.

Discussion.—DR. W. S. TEGNER (*London*) said that Hench had been interested in osteo-arthrosis. In 1938 he *x*-rayed all the joints in the body of an old lady of 104 years and found no osteo-arthrosis. None of her family had died below the age of 80. He *x*-rayed some of them and found no osteo-arthrosis in them either. He also *x*-rayed one or two other families of centenarians with the same results. When asked why he did not publish his findings he said that he could not get a statistically significant series of centenarians.

PROF. E. G. L. BYWATERS (*London*) asked how the joints were grouped.

DR. LAWRENCE replied that he had taken each type of joint as a group (*e.g.* T.I.P., P.I.P.) and regularly *x*-rayed thirteen groups of joints in hands, feet, cervical and lumbar spine, knees, and pelvis.

DR. V. WRIGHT (*Leeds*) asked how the low probability figures were calculated.

DR. LAWRENCE replied that they were calculated by a statistician by routine methods.

DR. A. J. BOLLET (*Charlottesville, Va*) observed that Sokoloff crossed mouse strains, 1 year old, with and without osteo-arthrosis, and found that a single recessive gene was responsible. Studies of biochemical changes in these animals as they developed osteo-arthrosis were in progress.

Serum Uric Acid Levels in a Random Population Sample. V. HEWITT (*Manchester*): Serum uric acid was estimated by an enzymatic technique in 433 males and 474 females drawn as a random sample of the population in Wensleydale, Yorkshire, covering all ages from 15 years upwards.

Before the survey was carried out, serum uric acid was also estimated by a colorimetric technique in 138 males and 150 females of the 55-64 age group drawn as a 1 in 10 random sample from the town of Leigh, Lancs. 57 sera were analysed by both methods and it was found that the colorimetric technique gave results which were on average 0·5/100 ml. higher than those obtained by the enzymatic technique.

Results in the total male population studied in Wensleydale showed that the modal value for serum uric acid lay between 4 and 4·5 mg./100 ml., with an arithmetic mean of 4·5 mg./100 ml. A detailed analysis of the distribution by age indicated that these values were relatively constant throughout life.

The total female population of Wensleydale showed lower values for serum uric acid distribution than were found in males. Detailed analysis showed this difference to be more pronounced in the 15-44 age groups where the modal value for serum uric acid lay between 3·0-3·5 mg./100ml. with an arithmetic mean of 3·5 mg./100ml. The 95 per cent. limits of normal distribution extended from 2-5 mg./100 ml. Between the ages of 45 and 54 years in females a transition phase developed and the mean serum uric acid rose rapidly so that values in the older age groups in women were similar to the corresponding values found in males. After age 55 years in females the modal value lay between 3·5 and 4 mg./100 ml., with an arithmetic mean of 4 mg./100 ml. The 95 per cent. limits of normal distribution extend from 2·0-5·9 mg./100 ml.

A similar trend was found in the smaller sample

* Published in the June, 1960, issue of the *Annals*, p. 95.
† To be published in the March, 1961, issue of the *Annals*, with discussion thereon.
‡ Published in the September, 1960, issue of the *Annals*, p. 243.
§ Published in the December, 1960, issue of the *Annals*, p. 361.

drawn from Leigh, where there was also little difference between the distribution of serum uric acid values in males and females at that age. The results of the survey were higher than the values found in Wensleydale, but this would most certainly be due in part to the different analytical techniques employed.

Discussion.—DR. B. ANSELL (*Taplow*) asked whether renal function had been investigated. In the hyperuricaemic males in Leigh, two of 24 had a raised blood urea level.

DR. HEWITT replied that this had not been done.

DR. A. J. BOLLET (*Charlottesville, Va*) said they had had a surprising experience in Detroit some years before in a large city hospital: A quarter of the gouty patients were women instead of the usually accepted sex ratio of 9:1. They were able to convince themselves that they were diagnosing the same disease in both sexes as regards tophi, radiological findings, age at onset, involvement of the great toe, response to colchicine, etc. There was a high proportion of Negroes and it was found that the incidence of gout among them was the same as in the white hospital population, in spite of a statement from Rochester, Minnesota (where there are very few Negroes) that the disease was rare in Negroes. He asked whether other workers had often seen gout in females?

DR. J. S. LAWRENCE (*Manchester*) said that perhaps their sample had been too small. Among 1,000 males and 1,000 females they had found 0·3 per cent. gout in males and none in females.

DR. R. HARRIS (*Buxton*) said that it was known that there was quite a lot of inbreeding in the villages of Wensleydale. He asked whether any family studies had been done? He had found a muscular dystrophy confined to certain Derbyshire villages, and not occurring in the surrounding country. He asked whether the geographic distribution of serum uric acid values in Wensleydale had been studied?

DR. J. S. LAWRENCE said that family studies were in progress but had not been analysed by villages. In any case, the villages lay very close together.

Rheumatoid Serum Factor in Extracts of Skin and Other Tissues. J. BALL (*Manchester*): In order to determine whether rheumatoid factor was present in the extravascular compartment, tissues from rheumatoid subjects were frozen, powdered, and serially extracted with volumes of 0·2 M NaCl equivalent to three times the wet weight (g.) of the tissue (ml.). The pooled extracts were titrated with sheep erythrocytes sensitized with anti-sheep erythrocyte serum, and the serum content of the pool estimated from its haemoglobin content. The dilution of the serum in the pool multiplied by the agglutinating titre of the pool was taken as the "equivalent titre", *i.e.* the titre which the subject's blood would need to have if the activity of the pool were merely a measure of the blood content of the extracted tissues.

In ten experiments, including healthy skin and tendon and subcutaneous nodules and joint tissues, the extractable activity (*i.e.* the titre of the pool) was positively correlated with the subject's blood serum titre. The "equivalent titre" was estimated in eight of these and was found to be between 4 and 26 times the serum titre. The discrepancy was of the same order in healthy skin and joint tissues.

It was concluded that the extractable activity could not be accounted for solely by the blood in the tissues. Since there was evidence that the healthy capillary seriously hindered the passage of serum agglutinating factor into the tissues, the results with apparently healthy skin raised the possibility that rheumatoid factor might be synthesized in the extravascular compartment.

Discussion.—DR. W. R. M. ALEXANDER (*Edinburgh*) said that he had compared the titres of heterophil antibody, isoagglutinins, and rheumatoid factor in 47 synovial fluids with the corresponding titres in the serum, and had found that the titres in the two former were usually one tube less than those in the serum, but there was much greater variability of the titre of rheumatoid factor. He asked if they had any data on the heterophil antibody titres of their extracts.

DR. BALL said that the extracts were absorbed with normal sheep cells and heterophil antibody was shown to be absent after absorption but no attempt was made to titrate heterophil antibody.

DR. A. G. S. HILL (*Stoke Mandeville*) asked if they had any data on non-rheumatoid subjects?

DR. BALL replied that they had none at the moment. In the present experiment they were comparing "normal" and diseased tissues in rheumatoid patients. Non-rheumatoid tissues were also being studied and they hoped to report the results later.

PROF. E. G. L. BYWATERS (*London*) said that, in a conversation with Dr. Morris Ziff, he had been given to understand that there was some evidence that agglutinating factor might be adsorbed to the walls of the capillaries. This might affect the interpretation of their results.

DR. BALL said that, if this were true, it would certainly be an important factor and might explain some of the findings, but they would still be left with the problem of the apparent similarity between normal skin and diseased tissues in the rheumatoid subjects.

A Controlled Trial of the Effect of a Period of Complete Immobilization of the Joints in Rheumatoid Arthritis. R. E. H. PARTRIDGE and J. J. R. DUTHIE (*Edinburgh*): Forty patients were admitted to hospital for 6 to 8 weeks, and all were given 60-80 gr. calcium aspirin daily. The patients were randomly allocated to two groups: twenty patients were immobilized in plaster splints in bed for 4 weeks, and no other form of treatment was used. The other twenty patients, a control group, were confined to bed for 4 weeks, and treated with maintenance exercises, rest splints, and physiotherapy. Subsequently both groups were treated along similar lines; weight-bearing was resumed and more active forms of physiotherapy were employed. Functional capacity, disease activity, and the range of joint movement in the two groups were assessed on admission, and at 4, 6, 12, and 24 weeks after admission. The results indicated some advantage for those patients completely immobilized, but the small numbers involved did not permit statistical analysis. There was no suggestion of the development of ankylosis in any of the completely immobilized joints.

Discussion.—DR. M. THOMPSON (*Newcastle upon Tyne*) said that the numbers in the trial were very small and he doubted whether it was worth submitting them to statistical analysis. Immobilization of the type described created great social and domestic problems. He asked whether any particularly good results had been obtained with individuals, to give a guidance for the selection of patients?

DR. PARTRIDGE agreed that the numbers in Grades 3 and 4 were too small. Some less severely affected patients did surprisingly well.

PROF. E. G. L. BYWATERS (*Taplow*) said that this was the first good study of a problem they had all wanted to tackle. There were apparently no black-and-white answers regarding the differences between the two groups, and he noted that the exercise group started at a considerable statistical disadvantage. While in this sort of patient a 4-week immobilization did not do any great harm apart from consuming 4 weeks of his life, in a child with a rheumatoid joint immobilized for 3 to 4 months, ankylosis or limitation was frequently seen. He felt that in such cases the immobilization might be the major damaging factor, This was a word of caution. The effect of rest on the disease itself appeared to be worth exploring further, since it might be that the disease only occurred where it did because of the movement of the joints.

PROF. S. J. HARTFALL (*Leeds*) asked what the procedure was in cases of elbow or knee deformity?

DR. PARTRIDGE replied that they used serial plasters, changed every 7 to 10 days, for knee deformities, but had not attempted to correct elbow deformities.

DR. R. HARRIS (*Buxton*) said that he had a similar study in progress. He splinted continuously only one of a pair of symmetrically involved joints, a removable splint being used for the other. It was hoped thus to find out which type of joint could safely be immobilized and which not.

DR. J. T. SCOTT asked how changes in grade were made when there was improvement in one criterion (*e.g.* erythrocyte sedimentation rate) and deterioration in another (*e.g.* haemoglobin level).

DR. PARTRIDGE replied that the erythrocyte sedimentation rate was usually the deciding factor and that clinical joint activity was also taken into account.

PROF. J. H. KELLGREN (*Manchester*) said that their aim had been to compare complete and partial immobilization. One would not expect a great difference in this. He thought that the real question was whether patients with rheumatoid arthritis should be advised to "keep going" and to exercise their joints as much as possible or to rest in bed with splintage of appropriate joints. In such a study a striking difference might emerge, which could be used to persuade the Ministry of Health to provide the "sanatorium" facilities that most of them agreed were needed. He asked whether those who came out of plaster in the study had sufficiently expert treatment so that they did not forget how to use their joints, as sometimes happened when people were sent to bed without expert supervision?

DR. PARTRIDGE replied that when the patients came out of plaster they were stiff for 3 to 4 days and needed and were given expert guidance to get their joints working again.

PROF. S. J. HARTFALL (*Leeds*) said that if normal joints were immobilized they were stiff for 24 to 48 hours.

PROF. E. G. L. BYWATERS asked whether the patients' weights were recorded.

DR. PARTRIDGE said that this was done. The patients were under different dietary regimes, some for obesity. The mean weights were about the same in the two groups at the start and finish of the trial.

PROF. E. G. L. BYWATERS asked what the effect of rest on muscle action was, and whether there was any atrophy.

DR. PARTRIDGE said that there was no greater loss of muscle power in the immobilized patients.

DR. J. H. GLYN (*London*) asked whether the ankles were completely immobilized, and whether the danger of ankylosis was greater in some joints than others. Did it result primarily from the inflammation or did it occur only in association with gross cartilage destruction?

DR. PARTRIDGE said that they had paid less attention to resting the ankles. As regards ankylosis, a significant loss of movement occurred in one patient in the rest group with much damaged knees. He had also had the experience of one case outside the trial in which one knee ankylosed completely after reduction of flexion deformity. Ankylosis was said to occur commonly in the wrists, but this did not occur in the trial. It would probably turn out that the initially non-crippled patients did best.

Heberden Round, 1960.—A meeting of the Society was held in the Bearsted Clinical Theatre of The London Hospital, on the occasion of the Heberden Round for 1960. The President, Dr. F. Dudley Hart, was in the chair.

"A Historical Note on Reiter's Disease" was presented by Dr. R. M. Mason (*London*). Although Hans Reiter was credited with the first description of the syndrome bearing his name in 1916, Feissinger and Leroy also published a paper in the same year describing this condition. As long ago as 1818 Benjamin Brodie had recorded the case histories of patients suffering from urethritis, acute polyarthritis, and ocular lesions and had recognized that these were associated. Astley-Cooper had also considered, in 1824, that rheumatic illness could complicate gonorrhoea.

Dr. V. L. Steinberg (*London*) then presented a clinico-pathological description of a severe case of rheumatoid neuropathy, with multiple systemic lesions due to rheumatoid disease.

A paper on "Placebo Reactors, with especial reference to Experiments with Control Substances", by Dr. C. R. B. Joyce (*London*) was presented by Dr. B. G. Adams, in the absence of the author.*

The Heberden Round for 1960 was presented by Dr. W. S. Tegner of The London Hospital. This

* To be published with the discussion thereon in the March, 1961, issue of the *Annals*.

Round maintained the clinical tradition established by predecessors, and consisted of the presentation of eight patients who suffered either from a rare rheumatic complaint or who had been referred to Hospital with an unusual presentation of a rheumatic condition. The presentation was both lively and witty and was acknowledged by the Society with hearty applause. The President thanked Dr. Tegner for his excellent demonstration and the Board of Governors of The London Hospital for providing tea and the venue of the meeting.

EMPIRE RHEUMATISM COUNCIL EXHIBIT ON REITER'S DISEASE

This Exhibit, which had gained first prize at the British Medical Association Exhibition at Torquay, 1960, was displayed in The London Hospital during this meeting.

AUSTRALIAN RHEUMATISM ASSOCIATION

FOURTH ANNUAL REPORT, 1960

At the fourth annual general meeting, held at the John Curtin Medical School, Canberra, on October 26, 1960, the president announced that the Australian Rheumatism Council had received a bequest of £100,000. Dr. J. E. Jefferiss had been awarded a travelling fellowship of the Empire Rheumatism Council to study in Great Britain. Dr. N. Wing, Dr. S. Nelson, Dr. R. F. A. Strang, and Dr. G. Burnison had attended the 8th World Congress of the International Society for the Welfare of Cripples in New York, the 3rd International Congress of Physical Medicine in Washington, and a meeting of a World Commission on Arthritis.

Several research projects had been carried out in Australian centres during the year.

Dr. F. May proposed that a fund be established by the A.R.A. for the purpose of aiding research or for the assistance of workers in the field of rheumatology, this fund to be called the Australian Rheumatic Foundation.

At a series of clinical meetings the following papers were presented:

Dr. F. May	Infective Arthritis.
Dr. Milazzo	Manifestations of Polyarthritis in the Feet.
Dr. B. Haynes	The Hip Joint in Rheumatoid Arthritis.
Dr. I. Ferguson	Serology of Polyarthritis.
Dr. R. G. Robinson	Urinary Chromatography in Collagen Disease.
Dr. R. F. Strang	Epidemiology of Rheumatism.
Dr. J. Dick-Smith	Corticosteroids in Rheumatoid Arthritis.
Dr. K. Coorey	Manifestations of Polymyalgia Rheumatica or Central Polyarthritis.
Dr. D. Lowther	Aetiology of Rheumatoid Arthritis.
Dr. B. Haynes	Electro-encephalogram in Rheumatoid Arthritis.
Prof. Sir John Eccles	Discussion.
Dr. J. Webb	Applied Anatomy and Pathology of the Intervertebral Disk.
Dr. F. May	Management of Lesions of the Cervical Spine.
Dr. J. Webb	Pulmonary Manifestations of Rheumatoid Arthritis.
Prof. Ogston	Synovial Fluid—A Lubricant.
Dr. M. Morris	Felty's Syndrome.
Dr. S. Nelson	Surgical Treatment of Arthritis.

Meeting of the Australian Association of Physical Medicine and Rehabilitation

Dr. G. Rich	Ultra-Sonics.
Dr. L. Wedlick	Development of a Rehabilitation Centre.
Dr. N. Wing	Rehabilitation.
Dr. S. Nelson	Report of the International Congress.

ST. BARTHOLOWMEW'S HOSPITAL

A department of Rheumatology is being formed at St. Bartholomew's Hospital, London. Dr. H. Wykeham Balme, F.R.C.P., has been put in charge of the clinic and proposes to establish an associated centre at Whipps Cross Hospital.

Ann. rheum. Dis. (1960), **19**, 384.

ABSTRACTS

This section of the ANNALS *is published in collaboration with the two abstracting Journals,* ABSTRACTS OF WORLD MEDICINE, *and* OPHTHALMIC LITERATURE, *published by the British Medical Association.*

The abstracts selected for this Journal are divided into the following sections: Acute Rheumatism; Chronic Articular Rheumatism (Rheumatoid Arthritis, Osteo-Arthritis, Spondylitis, Miscellaneous); Disk Syndrome; Gout; Pararheumatic (Collagen) Diseases; Non-Articular Rheumatism; General Pathology; ACTH, Cortisone, and other Steroids; Other General Subjects. At the end of each section is a list of titles of articles noted but not abstracted. Not all sections may be represented in any one issue.

The section "ACTH, Cortisone, and other Steroids" includes abstracts and titles of articles dealing with research into the scope and modus operandi *of steroid therapy.*

Acute Rheumatism

Comparison of the Recurrence Rate of Rheumatic Carditis among Children receiving Penicillin by Mouth Prophylactically or on Indication. LIM, W. N., and WILSON, M. G. (1960). *New Engl. J. Med.*, **262**, 321. 16 refs.

The difficulty of maintaining continuous chemoprophylaxis with penicillin in children with a past history of rheumatic fever, together with certain theoretical considerations, led the authors to investigate the value of such prophylaxis compared with that of penicillin treatment given on clinical indication alone.

The study was carried out over a 6-year period on children who had at least one observed attack of rheumatic carditis and were attending the Cardiac Rheumatic Clinic of the New York Hospital, 110 of whom received continuous prophylaxis (Group 1) and 103 penicillin therapy for 10 days only when indicated by the onset of a respiratory infection or signs of faucial inflammation (Group 2). The selection of the groups was not made at random, children with recent carditis usually being given continuous prophylaxis, while transfers from one group to the other also occurred. Group 2 contained a higher proportion of older children (13 to 16 years) than Group 1.

The recurrence rate of rheumatic carditis was found to be 6·6 per 1,000 patient-months in Group 1 and 2·9 per 1,000 in Group 2. This difference was found to be due to the greater number of more susceptible children with recent attacks in Group 1. There was no significant difference between the recurrence rates in different age groups in either group. Altogether seventeen recurrences were observed in Group 1 (associated with chorea in seven cases and polyarthritis in nine) and eight in Group 2 (with chorea in three cases and polyarthritis in five). Spot throat cultures in Group 1 revealed the presence of β-haemolytic streptococci in nine of 98 children who had sore throats; none of these relapsed, whereas in throat swabs from ten children who relapsed no β-haemolytic streptococci were found. In Group 2, of 94 spot cultures from children with sore throats, β-haemolytic streptococci were isolated from fifteen, while of six throat cultures from patients with recurrences, β-haemolytic streptococci were isolated from five.

Although it is agreed that there has been a great decline in the incidence of rheumatic fever in recent years, the authors point out that this decline antedated the antibiotic era and has not been accelerated since. They conclude that for children under close medical supervision continuous oral penicillin prophylaxis has no advantage over adequate penicillin therapy as indicated. Indeed it remains possible that the recurrence rate in this trial would have been the same if no penicillin had been given at all.

[This is a challenging paper. Nevertheless, the authors' conclusions should not be accepted without fuller proof. The two groups were not comparable, and subclinical streptococcal infections were not looked for by estimation of the antistreptolysin-O titre. It is of interest that β-haemolytic streptococci were isolated from nine children receiving continuous prophylaxis, none of whom developed rheumatic fever, whereas of fifteen children in Group 2 from whom β-haemolytic streptococci were isolated, eight suffered a recurrence of their rheumatic carditis.] *John Lorber.*

Studies of Blood Lipid Fractions of Quiescent Rheumatic Fever Patients and Their Siblings. APPLETON, H. D., COBURN, A. F., and MELTZER, Y. L. (1959). *Clin. Chem.*, **5**, 557. 13 refs.

It has been claimed that in rheumatic fever the fasting serum level of lipoprotein streptolysin-S inhibitor is significantly lower than normal, even during the quiescent phase of the disease. This study reported from New York Medical College and Metropolitan Hospital, New York, was designed to determine whether rheumatic fever is associated with abnormalities in the serum lipid level which might be due to genetic or environmental factors. It was found that in rheumatic children under the age of 14 years in whom the disease had been quiescent for one year, the mean non-fasting lecithin plasma level (2·76 mMol. per litre) was significantly lower than in their healthy siblings (3·15 mMol. per litre) living

under similar environmental conditions. The part played by constitution, heredity, and the disease in bringing about this difference is unknown [and its significance in aetiology is largely conjectural].

E. J. Holborow.

Beta-Hemolytic Streptococci and Rheumatic Fever in Miami, Florida. II. Antistreptolysin-O Titre Determinations between October, 1954, and May, 1955. STREITFELD, M. M., and SASLAW, M. S. (1960). *Dis. Chest*, **37**, 211. 16 refs.

An investigation is reported from the University of Miami School of Medicine, Florida, of the antistreptolysin-O titre in serial blood samples obtained from 236 school children during the winter of 1954-55. Blood was drawn in all cases at the beginning and end of the study. Throat swabs were obtained as a routine each month and whenever β-haemolytic streptococci were cultured, blood samples were withdrawn more frequently. In 48 out of a total of 472 blood samples the antistreptolysin-O titre was 250 or higher. The lowest average initial and final titres were found in children from whom no streptococci or only Group-B organisms were isolated and the highest in those in Group-A organisms. Infection with streptococci of Groups C and G were accompanied by moderate increases in titre. A rising antistreptolysin-O titre in successive blood samples was observed in sixteen (29 per cent.) out of 55 children with typable Group-A strains, nine (27 per cent.) of 37 with non-typable Group-A strains, three (17 per cent.) of eighteen with Group-C organisms, and ten (9 per cent.) of 99 with negative throat swabs. Between 1953 and 1955 a general rise in antistreptolysin-O titre was observed among those children for whom data were available over the 2-year period. There were 57 incidents of Group-A streptococcal infection associated with a 2-tube rise in antistreptolysin-O titre, but none of the affected children developed rheumatic fever. The authors emphasize that the value of isolated and serial estimations of antistreptolysin-O titre is limited and requires careful assessment.

Allan St. J. Dixon.

Coincidence of Patent Ductus Arteriosus and Rheumatic Heart Disease, with a Comment on the "Post-commissurotomy Syndrome". BOONE, J. A., and ROSEMOND, R. M. (1960). *Amer. J. Med.*, **28**, 247. 5 refs.

The frequent occurrence of rheumatic heart disease in patients with an interatrial septal defect is well known, but the association of such disease with other cardiac anomalies has been less often mentioned. In this paper from the Medical College of South Carolina, Charleston, the authors report that among 36 patients operated on for patent ductus arteriosus and followed up for 2 to 7 years were six in whom cardiac murmurs were absent immediately following ligation of the ductus but became audible one to eight days postoperatively and thereafter persisted or in some cases progressed. After further study four of these six patients were thought to have definite and two to have probable but less certain rheumatic heart disease. Detailed case reports are presented.

The authors were impressed with this apparently frequent coincidence in their series and review some of the literature on the co-existence of rheumatic heart disease with various congenital heart lesions. They suggest that there may be an increased susceptibility to rheumatic carditis in all patients with congenital heart defects, and that this provides further evidence that the "post-pericardiotomy syndrome", occurring as it does sometimes after operations for congenital cardiac defect as well as after valvotomy for rheumatic valvular disease, may indeed as has been suggested be due to reactivation of the rheumatic fever. They therefore propose, as a practical implication of their study, that prophylaxis with antibiotics as a routine might be as desirable in congenital cardiac conditions as in rheumatic heart disease and that postoperative follow-up should be prolonged.

[To further this interesting speculation the authors will need to provide much fuller data in a larger series of patients. This relatively small study is unconvincing.]

Celia Oakley.

Prophylactic Use of Oral Penicillin in Rheumatic Fever, Chorea, and Carditis. COPE, S., SANDERSON, G., ST. HILL, C. A., and CHAMBERLAIN, E. N. (1960). *Brit. med. J.*, **1**, 913. 6 refs.

The incidence of rheumatic manifestations, of intercurrent respiratory infections, and of laboratory evidence of streptococcal infection was studied during a 3-year period at St. Joseph's Children's Heart Hospital, Rainhill, Liverpool. Most of the children were convalescent from rheumatic fever. For the first year no prophylactic treatment was given. During the second and third years phenoxymethylpenicillin (penicillin V) (60 mg. twice daily) and benzylpenicillin (penicillin G) (200,000 units twice daily) respectively were given. Throat swabs were cultured and blood was taken for estimation of the antistreptolysin-O (ASO) titre and erythrocyte sedimentation rate (E.S.R.) at fortnightly intervals. During the first year (control period) out of 38 children, three developed typical rheumatic fever and two less definite rheumatic fever. During the second year, one out of forty had typical and three less well-defined rheumatic fever. In the third and last year, only one case of typical rheumatic fever occurred among 39 children. The cases of chorea numbered three, two, and one respectively. Rheumatic carditis without other manifestations of rheumatic activity developed in one child during the second year and in one during the third. [Not a well-defined category: one child had a raised ASO titre and another erythema marginatum in addition to the cardiac signs, which consisted in heart failure in children with established valvular disease.]

Six children developed acute bronchitis during the first year, six during the second, and three during the third. Not all children considered to have active rheumatism had a raised E.S.R. Group-A β-haemolytic streptococci was found on only a single occasion (from a child taking benzyl-penicillin) and no child had typical tonsillitis. Two children showed a prolonged rise of the ASO titre during the control period in addition to those considered to have rheumatic fever, as did eight

during each of the two treatment periods. Good blood penicillin levels were found with phenoxymethylpenicillin, but in spite of this the clinical results were poor. Higher and more sustained levels were obtained with the bigger dose of benzylpenicillin and the results were better, though the difference was not significant.

The frequency of high ASO titres in the absence of β-haemolytic streptococci on the throat swabs remains unexplained [but the throat swabs were not plated out fresh, but were taken to another hospital for that purpose.]

[This paper does not deal with the general management of children in the convalescent stage of rheumatic fever or during relapses. It does appear, however, that children are kept in hospital for very long periods and that steroid treatment is not used regularly.]

John Lorber.

Curative and Preventive Treatment of Rheumatic Fever. [In Russian.] KASSIRSKIJ, I. A., IVANOV, K. P., RYŽKOVA, N. P., KOŽUHOVA, V. K., PETROVA, L. M., and TARON, M. F. (1960). *Klin. Med.* (*Mosk.*), **38**, 24. 3 figs, 14 refs.

Rheumatic heart disease in all its stages can be successfully treated on the same principles as other chronic allergo-infective diseases, such as tuberculosis and syphilis. Corticosteroid hormones in combination with antibiotics are the most potent therapeutic agents in such cases and are indicated also in the presence of cardiac failure, particularly in the young.

The therapy advocated often results in remissions and in prevention of recurrences and of progressive lesions of the cardiac valves. Therapeutic failures are due to already established irreversible rheumatic collagenosis and permanent sclerosis. *A. Orley.*

Declining Severity of Rheumatic Fever: a Comparative Study of the Past Four Decades. BLAND, E. F. (1960). *New Engl. J. Med.*, **262**, 597. 3 refs.

In an attempt to determine the change which has taken place in the severity of rheumatic fever during recent years the clinical records were studied of the first 100 cases admitted in a first attack to the House of the Good Samaritan, Boston, during each of the years 1921-22, 1930-31, 1940-41, and 1950-51. All patients were under 20 years, the majority being under 10 years. There was a slight decrease in the incidence of carditis as judged by evidence of valvular disease, the incidence being 75 per cent. in 1921-22 and 60 per cent. in 1950-51. However, if the severity of the carditis was assessed in terms of cardiac enlargement there was a much more striking change. Of the 75 patients with carditis in 1921-22, 23 (30 per cent.) had marked cardiac enlargement while only fifteen (20 per cent.) had no enlargement of the heart. By contrast, in 1951-52, there was no cardiac enlargement in 28 (45 per cent.) and only in eight (14 per cent.) was it marked. Of the 100 patients admitted in 1921-22, 24 were dead within 5 years, whereas only three of those admitted in 1951-52 died within 5 years. The fall in the severity and mortality was gradual throughout the 40 years and was most marked towards the end of the 1930-39 decade, before the advent of penicillin. It is suggested that the most important factor responsible for the change was the considerable over-all improvement in the standards of living "of the poorer classes in urban areas". *C. Bruce Perry.*

Mimetic Features of Rheumatic-fever Recurrences. FEINSTEIN, A. R., and SPAGNUOLO, M. (1960). *New Engl. J. Med.*, **262**, 533. 23 refs.

In this paper from Irvington House and New Y rk University College of Medicine an analysis is presented of the manifestations of recurrent attacks of rheumatic fever in 161 patients observed in at least one attack for whom accurate information about initial and subsequent attacks was available. In 61 patients, who had a total of 129 attacks, and there was no clinical evidence of carditis in the first attack and the heart remained normal subsequently. In ninety patients, with a total of 211 attacks, the heart was clinically involved in the initial attack; in subsequent attacks the valvular damage "remained the same, recrudesced, or became worse". The remaining ten patients (thirty attacks) showed no cardiac involvement in the first attack but were found to have a significant diastolic murmur in recurrent attacks: it is suggested that in some cases at any rate the murmur may have been missed in the first attack. Non-cardiac manifestations of rheumatic fever were frequently repetitive in all patients. Joint involvement occurred in each of the 82 attacks in 39 patients, chorea alone in eight attacks in four patients, and carditis alone in twenty attacks in nine patients.

From their observations the authors consider that the major features of rheumatic fever tend to follow the same pattern in recurrent attacks and that this is particularly so in patients with valvular involvement. If valvular involvement is not present in the first attack it is unlikely to develop in subsequent attacks. In the majority of cases in which permanent rheumatic heart disease develops valvular involvement is present in the first attack. Changes in the P-R interval in the absence of a significant murmur have not the same significance. It is suggested that if these observations are confirmed it might be possible to modify advice on the duration of prophylaxis in certain patients, since recurrent attacks of rheumatic fever are particularly dangerous in those likely to develop carditis. *C. Bruce Perry.*

Antibody Titres in Acute Rheumatic Fever. [Review article.] WANNAMAKER, L. W., and AYOUB, E. M. (1960). *Circulation*, **21**, 598. 2 figs, bibl.

Paper Electrophoretic Studies of Glycoproteins in Rheumatic Fever. GORCZYCA, L. R., LAZARONI, J. A., JR., and MAIER, E. C. (1960). *Clin. Chem.*, **6**, 263. 1 fig., 15 refs.

Rheumatic Heart Disease: Résumé of a Chinese Medical Association Symposium. HWANG WAN, and MA WAN-SEN (1960). *Chin. med. J.*, **80**, 417.

Chronic Articular Rheumatism (Rheumatoid Arthritis)

Clinical Evaluation of Chloroquine in Rheumatoid Arthritis. La Tona, S. R., and Norcross, B. M. (1959). *Arch. interamer. Rheum.*, **2**, 595. 5 refs.

In this paper from the University of Buffalo Medical School, New York, the authors report an uncontrolled trial of chloroquine phosphate in the treatment of 145 unselected patients with rheumatoid arthritis in varying degrees of activity. The usual dosage was 250 to 500 mg. daily, and the duration of the trial was 6 to 18 months. Side-effects occurred in 41 patients, the commonest being nausea, dyspepsia, headache, dizziness, pruritis, and dermatitis; in thirteen patients these reactions were severe enough for administration of chloroquine to be stopped. Corneal changes developed in two patients. Improvement was noted in only 35 (31 per cent.) patients. No correlation was observed between the response to the drug and sex, age, or duration of the disease.

J. A. Cosh.

Research on the Behaviour, Nature and Meaning of the Rheumatoid Factor. [In English.] Robecchi, A., and Daneo, V. (1959). *Acta rheum. scand.*, **5**, 245. 28 refs.

In the first part of this paper from the Ospedale S. Giovanni Battista, Turin, the results of the Rose-Waaler test carried out on 3,050 occasions on 1,643 subjects, including patients with rheumatoid arthritis and various rheumatic and non-rheumatic diseases and healthy controls, are analysed in some detail. Sensitization of the erythrocytes was "reduced in intensity" in an attempt to increase specificity. With this modification agglutination at a dilution of 1:64 was regarded as a positive reaction.

Of 511 cases of rheumatoid arthritis, 63·9 per cent. gave a positive reaction to the test. Further analysis of these results showed that:

(1) no patient under the age of 15 years gave a positive response, the highest percentage of positive responses being found in middle age regardless of the duration of the disease;
(2) there was no significant difference in the behaviour of the response between the sexes;
(3) the proportion of positive results and the height of the titre increased with the duration of the disease, very high titres being found in cases in which a positive response had been obtained early in the disease process;
(4) there was a direct relationship between the intensity of the reaction and the severity of the radiological changes.

No clinical difference between cases giving positive and negative reactions could be detected, nor was any alteration attributable to treatment observed.

The results in numerous other pathological conditions are also reported [and are generally concordant with those of other authors]. In a control of 628 subjects (which included cases of osteo-arthritis and periarthritis) false positive results were obtained in 0·63 per cent. High agglutinating titres were found in two out of 23 cases of pulmonary silicosis. In a group of 99 cases of wholly non-rheumatic disease only two positive reactions were obtained. Relatives of patients with rheumatoid arthritis gave a positive reaction in 27·3 per cent. of cases compared with 8 per cent. in a control group. Comparison of the Rose-Waaler test with the Hyland drop latex test showed correlation in 82·7 per cent. of cases. However, this latex procedure gave 14·5 per cent. false positive results compared with 0·77 per cent. with the Rose-Waaler test.

The second part of the paper deals with various investigations directed towards the elucidation of the nature of this phenomenon. Eradication of any one of the four portions of complement did not remove the agglutinating capacity of serum. No success was obtained in the determination of a precipitation reaction. The authors found no evidence of hypersensitivity or immunization to heterologous globulins. The agglutinating factor was found in joint fluid and in the interstitial fluid.

Harry Coke.

Changes in the Digital Arteries in Rheumatoid Arthritis: a Study with the Aid of *post mortem* Brachial Arteriography. [In English.] Virtama, P. (1959). *Acta rheum. scand.*, **5**, 304. 7 figs, 9 refs.

The author performed post-mortem brachial arteriography in thirty cases at Kivela Hospital, Helsinki, Finland; ten of the subjects had been treated for rheumatoid arthritis. The mean age of the group was 65 years and the control series was chosen from the same age group. The brachial artery was injected with a suspension containing 100 g. barium sulphate and 180 ml. water. The hand was pressed between two plates of plywood joined together with four bolts and nuts and then radiographed. Uniform narrowness and tortuosity of the digital arteries was seen in both rheumatoid subjects and controls and was considered to be due to arteriosclerosis. The changes seen only in cases of rheumatoid arthritis were:

(1) local obliteration of the arterial trunks, particularly in the vicinity of the affected joint spaces;
(2) local post-stenotic shuttle-like dilatations of the arteries;
(3) hypervascularization and dilatation of arterioles close to bony erosions.

C. E. Quin.

Factors Precipitating and Predisposing to Rheumatoid Arthritis as illustrated by Studies on Monozygotic Twins. [In English.] Moesmann, G. (1959). *Acta rheum. scand.*, **5**, 291. 6 figs, 15 refs.

At Kommunehospitalet, Copenhagen, the author found four cases of rheumatoid arthritis occurring in monozygotic twins. A concordant manifestation of the disease was found in only one set. That the twins were monozygotic was confirmed by clinical examination and by blood grouping. In the twins concordant for rheumatoid arthritis the disease started at the same age. In the other three sets the twins were discordant for rheumatoid arthritis after observation periods of 21, 30, and 5 years

respectively. When these four sets of twins are added to 46 recorded in the literature data are available regarding fifty sets of monozygotic twins with rheumatoid arthritis affecting one or both members. The disease was concordant in eighteen and discordant in 32, so that the discordance rate is 64 per cent. The author points out that a discordance rate as high as this indicates the existence of an exogenous factor. Information on these fifty sets of twins was obtained from hospital departments or hospitals for rheumatic diseases, from general hospitals, from twins contacted by advertisements in the newspapers, and by contacting twins whose names had been obtained from parish registers. The concordance rate was found to be highest in those twins attending hospitals or departments for rheumatic diseases. A lower concordance rate was found in twins attending general hospitals and in twins who answered advertisements. It is considered that the mode of collection must have caused a selection mainly of concordant twins. This view is supported by figures for eight sets of monozygotic twins whose names had been obtained from parish registers. In these twins the discordance rate was 100 per cent. These findings suggest that the role of heredity in rheumatoid arthritis is negligible. *C. E. Quin.*

Rheumatoid Arthritis: Current Therapy and Medical Management. JOSSELSON, A. J. (1960). *Calif. Med.*, **92**, 326. 12 refs.

Rheumatoid Arthritis: Present-Day Physical Therapy. BAKER, F. (1960). *Calif. Med.*, **92**, 330. 16 refs.

Rationale of the Physiatric Management of Arthritis. ZANKEL, H. T. (1960). *Sth. med. J.* (*Bgham, Ala.*), **53**, 742. 2 refs.

Treatment of Rheumatoid Arthritis with Formaldehyde. (Traitement de la polyarthrite chronique évolutive par la formaldéhyde.) YVANOFF, J. (1960). *Scalpel* (*Brux.*), **113**, 531. 8 figs, 13 refs.

Mode of Action of Phenylbutazone in Rheumatoid Arthritis. (Über die Wirkung des Butazolidin bei der primär chronischen Polyarthritis.) WINER, J. (1960). *Praxis*, **49**, 649. 1 fig., 7 refs.

Treatment of Rheumatoid Arthritis with Phenylbutazone Observations of 980 Patients. (Leczenie gośćа stawowego butazolidyna [na podstawie obserwacij 980 chorych].) GIETKA, J. (1960). *Pol. Tyg. lek.*, **15**, 714. 39 refs.

Chrysotherapy in Rheumatoid Arthritis. A Long-Term Study of 435 Cases. (Chrysothérapie au cours de la P.C.E.) FORESTIER, J., CERTONCINY, A., and FORESTIER, F. (1960). *Lille méd.*, **5**, 247. 3 figs.

The Heart in Rheumatoid Arthritis. (Il cuore nell' artrite reumatoïde.) SCALABRINO, R., and CURTARELLI, G. (1960). *Reumatismo*, **12**, 1. 9 figs, 108 refs.

Subluxation of the Cervical Vertebrae in Rheumatoid Arthritis. (Remarques sur la luxation des vertèbres cervicales dans la polyarthrite rhumatoide.) COSTE, F., DELBARRE, F., CAYLA, J., and LAMBERT, P. (1960). *Sem. Hôp. Paris*, **36**, 1121. 16 figs, 17 refs.

(Spondylitis)

Some Effects of Ankylosing Spondylitis on Pulmonary Gas Exchange. RENZETTI, A. D., JR., NICHOLAS, W., DUTTON, R. E., JR., and JIVOFF, L. (1960). *New Engl. J. Med.*, **262**, 215. 13 refs.

Pulmonary function was studied in twelve male patients with clinical and radiological evidence of ankylosing spondylitis, but without lung or heart disease. It was found that vital capacity and total lung capacity were reduced but the maximum ventilatory capacity and the index of intrapulmonary mixing remained normal. Hyperventilation at rest and during and after exercise was observed in most of the patients, and there was mild arterial oxygen unsaturation in half of them. The percentage venous admixture was increased in five of the six patients so studied. It is suggested that the hyperventilation and the gas exchange defects might result from relative over-expansion of the lower and under-expansion of the upper portions of the lung.

K. C. Robinson.

Ankylosing Spondylitis in Two Families showing Involvement of Female Members Only. GRÖNVIK KORNSTAD, A. M., and KORNSTAD, L. (1960). *Acta rheum. scand.*, **6**, 59. 17 refs., 1 fig.

Rheumatoid Spondylitis with and without Arthritis. JULKUNEN, H., and KAIPAINEN, W. J. (1960). *Ann. Med. intern. Fenn.*, **49**, 17. 9 refs.

(Miscellaneous)

Clinical Picture of Rheumatic Thrombovasculitis. [In Russian.] HASIS, G. L., and SIGAL, E. S. (1960). *Ter. Arh.*, **32**, 24. 14 refs.

The authors describe sixteen cases of rheumatic thrombo-vasculitis occurring in eight male and eight female patients ranging in age from 14 to 56 years, several of whom had more than one attack. The vessels involved were the cerebral arteries in thirteen cases, the limb arteries in three, the pulmonary in three, the cardiac in two, the renal in two, and the intestinal in one. Three of the attacks took place during the first bout of acute rheumatism, nine during subsequent attacks, and the others during intervals between bouts. The outcome was satisfactory in thirteen cases, but proved fatal in three. Case histories of three of the patients are given, including two of those who died and came to necropsy. All the sixteen patients had cardiac lesions.

The authors state that the condition is much commoner than is realized and may often remain undiagnosed, especially in the milder latent forms. Histologically, the lesions consist of lymphoid infiltration of the arterial

walls (granular leucocytes are also often found), with thickening of the walls and clot formation in the lumen. In one of the fatal cases thrombosis of the abdominal aorta with gangrene of the left leg is described. They suggest that this complication of rheumatism deserves further investigation. *L. Firman-Edwards.*

New Concept of the Cause of Costen's Temporo-mandibular Arthrosis. COFFIN, F. (1960). *J. Laryng.*, **74**, 155. 4 figs, 11 refs.

The temporo-mandibular arthrosis described by Costen in 1934 may occur in later life in patients of either sex after removal of the molar teeth if there has been no satisfactory replacement, but this is really a secondary form. The primary condition typically occurs in women aged 15 to 30, usually in their early twenties. The author considers the symptoms to be due to a disturbance of joint function (with or without effusion, actual arthritis, and muscle spasm) which is secondary to a disturbance of bony growth of the mandible, skull, and/or maxilla, the amount or duration of growth of one part being out of relation to that of the other parts. In particular, growth in length and vertical height of the mandibular ramus may continue longer than the growth of adjoining structures; a corresponding inequality results if growth of the mandibular or maxillary alveolar elements or of the base of the skull ceases prematurely.

Clinically the diagnosis may be suspected if it is found that biting on a roll of cotton between the incisor teeth (that is, compressing the joint) increases the pain, while biting on the roll placed between the molar teeth (that is, "distracting" the joint) relieves the pain. The most popular method of treatment is to "raise the bite" by inserting a "platform" of acrylic resin between the occluding surfaces of the teeth, so relieving direct pressure on the joint. The author stresses that this interdental platform must not be too thick; its gradual removal, tooth by tooth round the mouth, may take up to 3 years. Injections of hydrocortisone into the joint help to allay inflammation and ease the pain. In no case has the author found it necessary to remove the articular disk or to divide the condylar neck. Post-mortem studies of 48 temporo-mandibular joints are described.

T. A. Clarke.

One Hundred Cases of Scapulo-humeral Periarthritis. (A propos de 100 cas de périarthrite scapulo-humérale.) JUNET, R. (1960). *Schweiz. med. Wschr.*, **90**, 313. 4 figs.

A short study of the clinical features and treatment of one hundred cases of scapulo-humeral periarthritis is presented. The incidence of this condition is high, constituting 15 per cent. of all cases of rheumatological disorders. It occurs twice as often in women as in men. It is unilateral in 71 per cent. of cases (right in 50 per cent., left in 21 per cent.) and bilateral in 29 per cent. Associated in one case in every three with osteo-arthritic manifestations, scapulo-humeral periarthritis may be regarded as a "tendinous" form of degenerative rheumatism. The evolution varies greatly from one case to another.

In regard to treatment the corticosteroids by the oral route should be reserved for very painful cases and should be administered for short periods only. Hydrocortisone and the other injectable steroids may be introduced into the scapulo-humeral joint, but preferably into the subacromial bursa. Since 1944 the author has used progressively increasing doses of tuberculin administered subcutaneously at weekly intervals. The results have been good on the whole, with few failures (5 per cent.). Undesirable secondary effects are rare and not dangerous. The therapeutic effect is attributed to stimulation of the adrenal cortex as indicated by Thorn's test.—[*From the author's summary.*]

New Salicylate Therapy for the Treatment of Arthritic Diseases. DENSON, L. J., and THOMPSON, W. R. (1960). *J. med. Soc. N.J.*, **57**, 314. 8 refs.

Gout

Clinical Experience with Zoxazolamine as a Uricosuric Agent in Gout. KOLODNY, A. L. (1960). *J. chron. Dis.*, **11**, 64. 1 fig., 6 refs.

Zoxazolamine is rapidly absorbed and is eliminated from the body in approximately 6 hours. It acts by inhibiting the tubular reabsorption of urates. Over a period of 27 weeks it was given in the treatment of acute intercritical, and chronic gout in eleven patients (nine male and two female). Pronounced uricosuric effects were obtained when a dose of 250 mg. was administered two to four times daily after meals and at bedtime. As regards diet, neither alcoholic nor purine foods were restricted in quantity. The daily intake of fluids ranged from 2 to 3 litres and when this was maintained it was not necessary to ensure that the urine was alkaline. There was some interference with the uricosuric action of the drug when salicylates were given concomitantly. On the other hand, phenylbutazone had an additive effect, as did probenecid though to a lesser extent than phenylbutazone.

In ten cases the clinical condition was either controlled or improved, but in the remaining case a urinary infection supervened and the patient died from uraemia. A maintenance dosage of 250 mg. twice daily resulted in diminution in the size of tophaceous deposits. Dizziness and nausea were the only recorded side-effects and were usually mild. The onset of nausea could be prevented by giving zoxazolamine during a meal. In three patients with renal damage acute attacks of gout developed during the early stages of treatment; these exacerbations subsided promptly following administration of colchicine. In spite of the loss of uric acid in the urine, no uric-acid stones were observed. *A. Garland.*

Suppression of Uric Acid Synthesis in the Gouty Human by the Use of 6-Diazo-5-oxo-L-norleucine. GRAYZEL, A. I., SEEGMILLER, J. E., and LOVE, E. (1960). *J. clin. Invest.*, **39**, 447. 5 figs, 25 refs.

At the National Institute of Arthritis and Metabolic Diseases, Bethesda, Maryland, 6-diazo-5-oxo-L-norleucine (DON) was administered to six patients with gout

and to one patient with renal urate lithiasis in order to observe its effect on uric acid production. In three patients the drug suppressed the incorporation of glycine-1-^{14}C into urinary uric acid. The absorption of glycine-1-^{14}C from the intestine was unaffected by DON, this finding supporting the view that in the dosage used the drug acts primarily by suppression of purine synthesis. Balance studies showed a reduction in serum urate levels and 24-hour urinary uric acid excretion in only two of the seven patients tested. The negative findings in the other five may have been due to the short duration of the balance studies and the presence of an expanded urate pool. The main toxic effects of the drug consisted in soreness of the mouth, sometimes with ulceration, and asymptomatic duodenal ulcers which healed promptly on medical treatment. No depression of the formed elements of the blood were seen. The high incidence of side-effects prevents the practical use of this particular compound in practice, but the possibility remains that more specific and less toxic inhibitors of purine biosynthesis may be found. *G. W. Csonka.*

Results obtained by the Administration of Sulphoxyphenylpyrazolidin (G 28 315) in 25 Cases of Gout. (Résultats obtenus par l'administration de sulfoxyphényl-pyrazolidine (G 28 315) chez vingt-cinq goutteux.) SERRE, H., SIMON, L., and CLAUSTRE, J. (1959). *Montpellier méd.*, **56**, 211. 7 figs, 10 refs.

The beneficial effect of salicylates and of probenecid in the treatment of chronic gout is well known. However, the effective dose of salicylates is close to the level of intolerance, and probenecid at times causes side-effects such as skin eruptions and gastric disturbance. Phenylbutazone is effective in acute gout, but its uricosuric effect is feeble.

In this paper from the University of Montpellier the authors describe the synthetic substance sulphoxyphenylpyrazolidin (G 28 315), a derivative of phenylbutazone, which has been shown to be strongly uricosuric. It is a white crystalline substance and is available for therapeutic use in tablets of 50 and 100 mg. They have employed this drug since 1958, and here report their results in 25 cases of gout and in six control subjects. The following dosage schemes were tried, the daily amounts being given in four equal doses at 3-hourly intervals:

(1) 400 mg. daily for 8 days followed by 600 mg. daily for the next 8 days;
(2) 800 mg. daily for 8 days and then 1,200 mg. daily for 8 days;
(3) 400 mg. daily for 5 days, 600 mg. daily for another 5 days, and 800 mg. daily for the last 5 days;
(4) 800 mg. daily for periods ranging from 12 to 30 days.

At each dosage level the blood and urinary uric acid concentrations were determined.

The best results were obtained by the administration of 800 mg. daily, nothing being gained by using a higher dose. In the patients receiving this dosage the mean blood uric acid level, which before treatment was 5·73 mg. per 100 ml., fell during treatment to 3·36 mg. per 100 ml. The initial mean urinary uric acid excretion was 751 mg. in the 24 hours, but during treatment this increased to a mean of 1,175 mg. per 24 hours. No such uniform response followed in the controls tested. A comparison with probenecid was made in one case only, in which under treatment with probenecid (1 g. daily) the mean blood uric acid level was 3·25 mg. per 100 ml., but when treatment with G 28 315 was instituted in a dosage of 800 mg. daily the level fell after 15 days to 2 mg. per 100 ml. and the urinary uric acid excretion rose from 741 to 932 mg. per 24 hours.

The authors conclude that G 28 315 is a valuable uricosuric agent, and probably the most powerful. In every case the blood uric acid level was reduced to about 4 mg. per 100 ml. or less. Gastric intolerance was never observed, and no patient suffered any toxic effects on the kidneys, blood, or skin. The drug did in a few patients precipitate an attack of acute gout.

Kenneth Stone.

Vibratory Sense and Oscillometric Index in Gout and in Rheumatoid Arthritis. DANOWSKI, T. S., MOSES, C., JR., and MARGOLIS, H. M. (1960). *Amer. J. med. Sci.*, **239**, 295. 5 figs, 7 refs.

A study of the threshold for the perception of vibration in gout and rheumatoid arthritis is reported in this paper from the University of Pittsburgh School of Medicine, Pennsylvania. Tests of perception were carried out with an electric vibrator, or biothesiometer, in which the rate of movement of a metal rod could be varied by increasing the input of the current. Oscillometric readings were also obtained. The patients with gout were taking $\frac{1}{100}$ gr. (0·65 mg.) of colchicine and 1·5 g. "benemid" (probenecid) daily. The patients with rheumatoid arthritis were receiving steroids of the adrenocortical type, phenylbutazone, gold salts, and physiotherapy.

An increased threshold for vibratory-sense perception was observed in all cases. The reason for this was not clear but it is suggested that in cases of gout the phenomenon could be attributed to vitamin deficiency secondary to treatment with uricosuric agents, and that in patients with rheumatoid arthritis neuropathy and adrenocortical steroid therapy were associated with the decreased acuity of the vibratory sense. No significant difference was observed between controls and patients with gout or rheumatoid arthritis in the mean oscillometric index.

A. Garland.

Lesions of Cartilage in Gout. (Le cartilage goutteux et ses lésions.) CABANNE, M. F. (1960). *Rev. lyon. Méd.*, **9**, 265. 3 figs, bibl.

This paper from the École Nationale de Médecine de Dijon presents an account of the histological features of cartilaginous lesions in gout. Extra-articular cartilage, such as that of the external ear, usually remains normal in gout, or is subject only to occasional and feeble infiltration by urates. In contrast, however, hyaline articular cartilage is characteristically involved: thus it may show either scattered foci of necrosis in areas of

urate deposition in the acute phase of an attack, or a variety of chronic changes as part of a "gouty arthropathy". In discussing the mechanism of the cartilaginous changes in gout the exact nature of which is still obscure, the author suggests that the initial deposition of urates in this tissue may be the result of its avascularity, its richness in sodium, or its mucopolysaccharide content, while the mutilating destruction of the cartilage seen in gouty tophaceous and ankylosed joints appears to result from extensive dissecting fibrosis of articular and periarticular tissues as well as from the direct effect of urate deposits.

H. A. Sissons.

Acute Gout during Chlorothiazide Therapy. McGEE, R. R. (1960). *Sth. med. J. (Bgham), Ala.*, **53**, 736. 1 ref.

Action of G28315 (Sulphoxyphenylpyrazolidin) in a Series of Patients with Gout. (Accion del G.28315 en una serie de enfermos gotosos.) GAUDINO, P. M., and FORT, H. J. (1960). *Arch. argent. Reum.*, **23**, 15. 4 figs, 8 refs.

Prophylaxis of Gouty Attacks by Means of Phenylbutazone. (Profilaxis de los ataques gotosos por medio de la fenilbutazona.) MORENO, A. RUIZ (1960). *Arch. argent. Reum.*, **23**, 21. No refs.

Pararheumatic (Collagen) Diseases

Anti-cytoplasmic Factors in the Sera of Patients with Systemic Lupus Erythematosus and Certain Other Diseases. DEICHER, H. R. G., HOLMAN, H. R., and KUNKEL, H. G. (1960). *Arthr. and Rheum.*, **3**, 1. 1 fig., 42 refs.

This complex study was carried out at the Rockefeller Institute, New York. Using extracts in normal saline of various animal and human organs as antigens the authors demonstrated complement fixation with sera from 33 out of 37 patients with systemic lupus erythematosus (S.L.E.), seven out of eleven patients with primary biliary cirrhosis, two out of three patients with Sjögren's syndrome, and one patient with scleroderma. Positive results were also obtained with eight of 35 normal sera, but in low titre. Sixteen sera giving positive reactions with saline extracts were then tested against five preparations containing isolated calf thymus nuclei, an extract of such nuclei in phosphate buffer, isolated calf liver mitochondria, microsomes, and a soluble cellular fraction respectively. Ten of these sera, from patients with S.L.E., all reacted positively with all five cellular preparations. In the case of the mitochondria and microsomes it was possible to exclude contamination with soluble nuclear material as a cause of the positive reactions since complement-fixation tests using the supernatant from the last wash of these constituents as antigen gave a negative result in each case. Of the other six sera tested against the cell fractions four were from patients with biliary cirrhosis, one from a patient with discoid L.E., and one from a case of Sjögren's syndrome. With these sera positive results were obtained against mitochondria and microsomes, but the results with the other preparations varied. However, the results with nuclear material always matched those with the soluble cellular fraction. In some cases control tests with ten normal sera gave low-titre ($<1:16$) positive results against mitochondrial and microsomal preparations only.

Further work with tissue extracts in various solvents and after treatment with certain enzymes suggested that a number of different cytoplasmic constituents were involved in these reactions, but that one of these constituents seemed to react only with S.L.E. sera. Electrophoresis of the test sera on starch medium and zone ultracentrifugation experiments showed that the antibody constituent of these reactions were γ globulins with a sedimentation constant of 7. (Some of the sera from patients with diseases other than S.L.E. contained additional active 19 S globulin.)

M. Wilkinson.

Heart in Systemic Lupus Erythematosus. BRIGDEN, W., BYWATERS, E. G. L., LESSOF, M. H., and ROSS, I. P. (1960). *Brit. Heart J.*, **22**, 1. 19 figs, 10 refs.

In the past 10 years the authors have studied, with particular reference to cardiac involvement, sixty patients with systemic lupus erythematosus (S.L.E.) who were seem at the Hammersmith Hospital, the London Hospital, and the Canadian Red Cross Memorial Hospital, Taplow. Clinical details are given, and the non-cardiac manifestations, the serological, and haematological findings, as well as the post-mortem findings in the 27 patients who died, are described.

Of these latter endocarditis was found at necropsy in over half, the mitral valve being involved in ten cases, the aortic valve in four and the pulmonary and tricuspid valves each once. The valvular lesion was primary in thirteen cases and in two there was a secondary superimposed bacterial infection. The primary lesions, which were of a type previously reported in the literature, occur commonly at the base of the valve, particularly in the valve pocket, and numerous endothelial cells, Antischow myocytes, and inflammatory mononuclear cells are present, the disintegration of these resulting in the formation of haematoxylin bodies and eosinophilic fibrinoid material. The myocardial fibres were seldom involved, but in one patient there was patchy degeneration of some fibres, the nuclei of which lost definition and resembled the inclusion body of an L.E. cell. Myocardial fibrosis with associated vascular occlusion was present in two patients, but myocardial abnormalities were mostly interstitial and sometimes extensive. A common finding was a fibrinoid lattice with cellular infiltration, many of these cells undergoing degeneration to haematoxylin bodies. In some cases, the fibrinoid lattice appeared to have formed on collagenous strands proceeding from an oedematous area of connective tissue. The authors consider that the characteristic fibrinoid change derives mainly from clotting of fibrinogen in areas of gelatinous exudate, but occasionally local cellular

infiltration occurs and the products of nuclear degeneration then contribute to the fibrinoid substance, which may thus differ in different diseases and even in different sites in the same organ. The pericardium was abnormal in twenty of the 27 patients coming to necropsy, the layers usually being obliterated. There was much fibrinoid change and many haematoxylin bodies.

The incidence of clinical cardiac manifestations is then discussed. Endocarditis is not recognized clinically so often as it is found at necropsy, since the organic murmurs are often soft and transient and the valvular lesion rarely results in significant obstruction or incompetence. The various murmurs elicited are described in detail, together with reproductions of illustrative electro- and phono-cardiograms. The aortic and mitral valves were found to be affected far more commonly than the valves of the right heart. Myocarditis was difficult to detect clinically because of its association with pericarditis, hypertension, and possible water retention as a result of corticosteroid therapy. In no case could heart failure be attributed solely to myocarditis. In the authors' experience pericarditis, a well-known complication of S.L.E., occurs in almost all patients at some stage of the disease. Of seven patients without necropsy evidence of pericarditis, five died exceptionally and suggestively early in the course of the disease. Pericarditis usually appears as an isolated or a recurrent attack and is frequently painless; no fewer than 52 patients showed electrocardiographic abnormalities consistent with acute or chronic pericarditis at some stage of the disease.

During the disease 26 patients developed a diastolic blood pressure of over 95 mm. Hg, which was attributed to renal disease in twenty cases. Corticosteroid therapy had been given to thirteen of these patients and occasionally aggravated the hypertension, but of the six patients with hypertension not due to renal disease four had received steroid therapy. Congestive heart failure developed in 22 patients, systemic hypertension being the main, but rarely the sole, cause; other contributory causes were pericarditis, fever, secondary infection, anaemia, and sodium and water retention. The response of the heart failure in these patients to sodium restriction, digitalis, and mersalyl was usually poor. In two cases an increase in the dosage of cortisone controlled the disease better and the heart failure improved, but generally the heart failure is made worse by administration of salt-retaining corticosteroids.

J. Warwick Buckler.

Desoxyribonucleic Acid (DNA)-Bentonite Flocculation Test for Lupus Erythematosus. BOZICEVICH, J., NASOU, J. P., and KAYHOE, D. E. (1960). *Proc. Soc. exp. Biol. (N.Y.)*, **103**, 636. 12 refs.

This paper from the National Institute of Allergy and Infectious Diseases, Bethesda, Maryland, describes another test for systemic lupus erythematosus (S.L.E.) depending on the affinity of L.E. serum for deoxyribonucleic acid (DNA). In this test, which is similar to the bentonite flocculation test for rheumatoid arthritis, bentonite particles are coated with DNA and bovine plasma albumin is added to prevent the particles from clumping. The addition of L.E. serum (not plasma) causes flocculation, but the reaction is more difficult to read than in the test for rheumatoid arthritis.

The DNA-bentonite flocculation reaction was positive in all of eight cases of active S.L.E. (in all of which the result of the L.E.-cell test was positive) and in two out of five cases of S.L.E. in remission (with a positive L.E.-cell reaction in four). The reaction was negative with 138 sera from patients without S.L.E. including six cases of rheumatoid arthritis with positive L.E.-cell reactions.

M. Wilkinson.

Hemagglutination Study of Serum Factors Related to L.E. Cell Formation. LEE, R. C., and EPSTEIN, W. V. (1960). *Arthr. and Rheum.*, **3**, 41. 1 fig., 29 refs.

In studies carried out at the University of California School of Medicine, San Francisco, L.E. factor was measured by its ability to agglutinate sheep's erythrocytes treated with tannic acid and coated with a nucleoprotein extract from calf thymus. Rheumatoid factor was measured by the agglutination of cells coated with Cohn Fraction II of human plasma.

All sera from ten cases of systemic lupus erythematosus agglutinated cells coated with nucleoprotein extract in titres up to 1:64,000, but only four of the sera agglutinated cells coated with Fraction II. All sera from ten patients with rheumatoid arthritis gave Fraction-II titres of 1:56,000 or higher, but none produced L.E. cells or agglutinated cells coated with nucleoprotein extract. Previous exposure of the treated cells to γ globulin inhibited Fraction-II haemagglutination, but not nucleoprotein-extract haemagglutination, whereas exposure of the treated cells to nucleoprotein extract inhibited nucleoprotein-extract haemagglutination but not Fraction-II haemagglutination. Deoxyribonucleic acid failed to inhibit nucleoprotein-extract haemagglutination. The formation of L.E. cells was inhibited by nucleoprotein extract, but not by γ globulin.

The authors consider that nucleoprotein-extract haemagglutination gives a quantitative measure of the serum factor responsible for L.E.-cell formation.

M. Wilkinson.

Evaluation of Methylprednisolone, Triamcinolone, and Dexamethasone in the Treatment of Disseminated Lupus Erythematosus. (Valoracion de la metilprednisolona triamcinolona y dexametasona en el tratamiento del lupus eritematoso generalizado.) JALIL M, J., GUERRERO A, R., and HARNECKER, J. H. (1960). *Rev. méd. Chile*, **88**, 12. Bibl.

At the Hospital San Juan de Dios, Santiago, Chile, the authors treated sixteen patients with systemic lupus erythematosus (S.L.E.) with methylprednisolone, ten with triamcinolone, and twenty with dexamethasone. The number of new patients, not previously treated with corticosteroids, were eight, five, and seven respectively. Doses were varied according to symptoms and patients were transferred to and from the corticosteroids previously employed. While the conditions of the trial did not permit a precise comparison, no consistent

superiority of any one of the newer corticosteroids emerged, and the considerable variation in patients' response to individual drugs was confirmed. The authors conclude that prednisone and prednisolone have not been displaced in the treatment of S.L.E., but individual differences in response justify a trial of the various steroids available.

Allan St. J. Dixon.

Testicular Lesions of Periarteritis Nodosa, with Special Reference to Diagnosis. DAHL, E. V., BAGGENSTOSS, A. H., and DEWEERD, J. H. (1960). *Amer. J. Med.*, **28**, 222. 4 figs, 13 refs.

In this study, undertaken at the Mayo Clinic to determine the value of testicular biopsy examination in the diagnosis of periarteritis nodosa, the authors have examined the records and histological sections of formalin-fixed blocks of the testes of 44 patients aged 11 to 71 (average 47) years seen at the Clinic during the period 1931-55, in thirty of whom the diagnosis of periarteritis nodosa was established or suspected. Abnormalities suggestive of the disease were found in 41 (93 per cent.) of these cases. Diagnostic arterial lesions were seen in 38 cases (86 per cent.), while less common changes included infarcts, degeneration or disappearance of the tubules, haemorrhage, and haematoma. Clinical abnormalities of the testis had been observed in only eight of the patients (18 per cent.), though the size had been recorded as subnormal in eleven (25 per cent.).

By sampling different sectors of the histological sections the authors made a rough estimate that positive diagnostic signs of periarteritis in a single testicular biopsy specimen could be expected in only about one in five male patients (22 per cent.). Testicular biopsy in the living patient is therefore recommended only when clinical findings suggestive of periarteritis are accompanied by testicular abnormalities and there are, moreover, no detectable cutaneous, subcutaneous, or muscular lesions. If biopsy is performed the specimen should include part of the tunica vasculosa as well as some of the underlying parenchyma.

A. Wynn Williams.

Ischemic Neuropathy in Necrotizing Arteritis. HOLT, G. W. (1960). *Neurology*, **10**, 43. 4 figs, 26 refs.

From the University of Colorado School of Medicine, Denver, the author describes one fatal case of periarteritis nodosa which followed cortisone therapy and a further case in which, however, the patient recovered on withdrawal of therapy; the lesions in the former case were confirmed histologically. In a review of the literature he has found 36 reported cases of arteritis occurring in rheumatoid arthritic patients treated with steroids. The three cardinal symptoms are progressive neuropathy, widespread multiple involvement of the organs, and constitutional reaction.

The author's first case occurred in a female patient aged 51 with a history of rheumatoid arthritis for 3½ years, during which she had received 25 to 75 mg. cortisone daily, together with supplements of other steroids, gold and salicylates. Burning and sensations of tingling developed in the hands, followed by wrist and foot drop. Progress was intermittent, but by the end of 6 months there was generalized paralysis and areflexia. Purpuric skin eruptions appeared, followed by gangrene, first of the rheumatic nodules in the hands and later involving the nail cuticle. The gangrene spread to include the finger tips and around the ankles. Patches of viable tissue in the midst of gangrenous areas suggested disseminated arterial lesions. At necropsy a necrotizing arteritis, indistinguishable from periarteritis nodosa, was found to be widespread in the viscera and particularly in the vasa nervorum of the vagus nerves.

The second case was seen in a 39-year-old woman with rheumatoid arthritis who had been treated for over 5 years with corticosteroids. She suffered from weakness and hypo-algesia of the extremities and showed loss of reflexes, cyanosis, and impending gangrene of the fingers and toes. The cortisone was withdrawn under cover of a week's treatment with ACTH (corticotrophin). A week later the punctate gangrenous lesions and the peripheral cyanosis had disappeared, the neuropathy showed some improvement, and the rheumatoid nodules also cleared up. Observation for a year has revealed no return of these signs and symptoms.

The author discusses the mechanism of arteritis in such cases and comes to the conclusion that it is a sensitization phenomenon related to the tuberculin and Herxheimer reactions.

William Hughes.

Renal Involvement in Progressive Systemic Sclerosis (Scleroderma). LEVINE, R. J., and BOSHELL, B. R. (1960). *Ann. intern. Med.*, **52**, 517. 3 figs, 20 refs.

The authors of this paper from Harvard Medical School and the Peter Bent Brigham and the Robert Breck Brigham Hospitals, Boston, describe five cases of scleroderma (progressive systemic sclerosis) in which acute renal failure caused death. Because the cases were selected no conclusions could be drawn concerning the incidence of renal involvement in scleroderma, but this is known to be present in the majority of cases examined post mortem. The classical skin changes of scleroderma were present in all five cases. The acute form of renal disease was characterized by rapidly advancing uraemia with, in some cases, hypertension, and death within a month. In one case there was evidence of preceding renal damage. Pathologically, the chief features were intimal proliferation of the small intralobular vessels, fibrinoid necrosis of the afferent arterioles and sometimes of the glomerular loops, and focal cortical infarction. In the more chronic form obliteration of the glomeruli and interstitial fibrosis occurred. These features were sometimes seen in the absence of hypertension. It is pointed out that lesions resembling those seen in other collagen diseases have also been described in cases of progressive systemic sclerosis. The authors emphasize the rapidly fatal outcome in the acute form of the disease, which appears to be little if at all affected by any currently available treatment.

G. L. Asherson.

Lesions of the Heart in Systemic Scleroderma. [In Russian.] GUSEVA, N. G. (1960). *Ter. Arh.*, **32**, 30. 2 figs, 26 refs.

Cardiac involvement in scleroderma was first described in detail by Weiss and others in 1943 (*Arch. intern. Med.*, **71**, 749), although a single case had earlier been reported by Heine in 1926 (*Virchows Arch. path. Anat.*, **262**, 251). In the present communication the author describes her investigations in fifteen cases (including four at necropsy), all the patients having cardiac symptoms of varying degree, including dyspnoea, tachycardia, precordial pain, and arrhythmia (extra systoles or gallop rhythm). Radiography revealed moderate enlargement of the heart to the left in seven cases, and unfolding of the aortic arch in ten; electrocardiographic changes present in fourteen cases consisted in low voltage in eleven, left-axis deviation in seven, right-axis deviation in six a widened QRS complex in five, S—T displacement in eight, and abnormalities of the T wave in thirteen. Pathological examination of the heart muscle in the four fatal cases revealed myocardial involvement by the sclerodermal process. The coronary arteries were intact, but the smaller vessels showed fibrinoid infiltration and narrowing of the lumen, and the muscle fibres adjacent to the patches of cardiosclerosis were hypertrophied. All layers of the heart were involved, and there was slight pericardial exudate. Mitral stenosis was present in all four cases, while there were lesions of the aortic valve in two cases and of the tricuspid valve in three.

The condition is sometimes mistaken for rheumatism and in five of the author's cases this was the first diagnosis. Subjective symptoms are often absent in the early stages. Treatment is unsatisfactory, but the prolonged administration of steroid hormones is insisted upon.

L. Firman-Edwards.

Systemic Lupus Erythematosus: a Review of Certain Current Pathogenetic Concepts. ALTROCCHI, P. (1960). *J. chron. Dis.*, **11**, 34. 2 figs, bibl.

Critical Evaluation of the Precipitation Reaction for Systemic Lupus Erythematosus. (Valutazione critica della reazione di precipitazione per il lupus eritematoso sistemico.) ORABONA, M. L., and SEMERARO, V. (1960). *Reumatismo*, **12**, 34. 6 refs.

Immunopathology of Lupus Erythematosus. MIESCHER, P. A., THOMAS, L., BENACERRAF, B., COOPER, N. S., FRANKLIN, E., and ROTHFIELD, N. (1960). *Brit. J. Derm.*, **72**, 221. 1 fig., 23 refs.

Progress in the Understanding of Lupus Erythematosus. GOLD, S. (1960). *Brit. J. Derm.*, **72**, 231. 1 fig., 43 refs.

Scleroderma (Progressive Systemic Sclerosis). OFSTAD, E. (1960). *Acta rheum. scand.*, **6**, 65. 4 figs, 37 refs.

Antimalarials in the Treatment of Dermatomyositis. WARD, R. W. (1960). *J. med. Soc. N.J.*, **57**, 317. 19 refs.

Incidence of the Gm Serum Groups in Collagen Diseases. TIILIKAINEN, A. (1960). *Ann. Med. exp. Fenn.*, **38**, 51. 10 refs.

Roentgenographic Aspects of Collagen Diseases. (Aspectos radiologicós en las enfermedades del colágeno.) CRESPO, D. I. (1960). *Arch. interamer. Rheum.*, **3**, 40. 44 figs, 41 refs.

General Pathology

Heparin-Latex Test in Rheumatoid and Non-rheumatoid Serums. DE FOREST, G. K., and BARBORIAK, J. J. (1960). *Proc. Soc. exp. Biol. (N.Y.)*, **103**, 115. 3 refs.

It has been reported by Gofton and others (*Canad. med. Ass. J.*, 1957, **77**, 1098; *Abstr. Wld Med.*, 1958, **23**, 454) that certain polysaccharides can be used in place of α-globulin to "sensitize" latex particles in the latex fixation test of Plotz and Singer. The present authors, working at Yale University School of Medicine, describe a modified latex fixation test agglutination in which heparin is used as the heterologous sensitizing agent and which they applied to ninety sera specially selected as likely to give false positive reactions by reason of having a high α-globulin content (over 20 per cent. of total protein) as determined by paper electrophoresis. The heparin-latex test gave 52 per cent. positive results as against 20 per cent. in the standard test, which gave 6·4 per cent. false positive results in a series of 313 unselected control sera. The authors conclude that the heparin-latex method offers no improvement in routine tests for rheumatoid arthritis.

[The investigation was undertaken on account of the fact that the definition of "rheumatoid factor" adopted by the Arthritis and Rheumatism Foundation "implies the obligatory presence of an 'outside' α-globulin in serological reactions in which the rheumatoid factor participates". It is difficult, however, to determine the source of this obligation in the official definition.]

Harry Coke.

Significance of Blood Serum Glycoprotein Estimations in the Evaluation of the Activity of a Rheumatic Process. [In Russian.] DUHOVNAJA, O. (1960). *Ter. Arh.*, **32**, 10. 2 figs, 26 refs.

The author reports the results of an electrophoretic study of the serum glycoproteins in 120 rheumatic patients and 33 healthy control subjects. In the controls glycoproteins were present in all plasma protein fractions, the highest content being in the α^2 globulins. In patients with active rheumatism the glycoprotein content in both the α^1 and α^2 globulin fractions was higher than in the controls, but in the albumin and β- and γ-globulin frac-

tions it was considerably lower. With the subsidence of rheumatic activity the proportions moved towards normal. These changes were more evident in the glycoproteins than in the protein fractions themselves, and this method is therefore regarded as being more sensitive for the detection of activity of a clinically inactive rheumatic process.

[A similar communication by Denisova writing from Kazan reports much the same findings, except that in some 33 per cent. of her active cases of rheumatism the γ-globulin glycoprotein content was also raised. She also reports a certain parallelism between the glycidograms and the proteinograms, but in 10 per cent. of her patients the latter remained normal, whereas the former revealed changes and is therefore considered to be more reliable.]

L. Firman-Edwards.

Precipitin Reaction between Rheumatoid Factors and Gamma Globulin: Studies by Double Diffusion in Agar. FRANKLIN, E. C. (1960). *Arthr. and Rheum.*, **3**, 16. 6 figs, 18 refs.

From New York University College of Medicine the author reports a study of the nature of the precipitin reaction which occurs between "aggregated" human γ globulin (Cohn Fraction II in 1 per cent. solution heated to 63° C. for 10 minutes) and sera showing agglutination to a titre of 1:1,024 or greater in the Rose-Waaler Test. Strongly positive agglutinating sera from 22 cases of rheumatoid arthritis, one case of sarcoidosis and one of "hyperglobulinaemic purpura" all gave precipitin lines on testing by the Oudin double gel diffusion technique. Separate precipitation lines between a rheumatoid arthritis serum and antisera to 7 S and 19 S γ globulin were demonstrated by immunoelectrophoresis, whereas the aggregated human γ globulin produced only a single precipitation line corresponding to the 19 S molecule [? beta-2-M].

By the Ouchterlony technique a reaction of identity was obtained by employing antisera to three different proteins produced in a number of different animal species. A number of experiments in which the Ouchterlony principle was employed were described, the results of which, in the author's opinion, indicate that both the 7 S and the 19 S γ globulins take part in the rheumatoid precipitin reaction. Identity of reaction by fusion of the precipitation lines was shown between both 7 S and 19 S γ globulins and rheumatoid sera, together with the two additional pathological sera mentioned. The immunological relationship was further studied by a new modification of the Ouchterlony diffusion method and compared with other known antigen-antibody reactions. Three of the 24 sera showed two precipitin lines on reaction with aggregated human γ globulin, and it is considered that "these findings appear to confirm the existence of at least two rheumatoid factors, one of which reacts with human and rabbit γ globulins, and one of which reacts primarily with human γ globulin".

[Knowledge of the antigenic constitution of the aggregated human γ globulin might be interesting here in view of the known possibility of six different proteins constituting γ globulins (Heremans) and the multiplication of antigens obtained in some proteins by heat (Shultze).]

Harry Coke.

Pyruvic Acid in the Blood and Synovial Fluid of Patients with Rheumatoid Arthritis. KALLIOMÄKI, J. L., MARKKANEN, T. K., PIRILÄ, A. M., and TOIVANEN, P. (1960). *Ann. Med. exp. Fenn.*, **38**, 148. 10 refs.

Proteolytic Enzymes of Synovial Fluid. VARTIO, T. (1960). *Ann. Med. exp. Fenn.*, **38**, 94. 17 refs.

Histological Findings from the Synovial Membrane and Surgical Treatment of Affected Joints in Rheumatoid Arthritis. KODAMA, T. (1960). *Acta rheum. scand.*, **6**, 48. 8 refs, 8 figs.

Structural Function of Mucopolysaccharide in Connective Tissue. FESSLER, J. H. (1960). *Biochem. J.*, **76**, 124. 26 refs.

Studies on Synovial Tissue. 7. Concentrations of Creatine and Phosphocreatine in Synovial Tissue. COOK, E. R., PAGE THOMAS, D. P., and DINGLE, J. T. (1960). *Biochem. J.*, **76**, 120. 12 refs.

Lymphangiography and Lymphadenography of the Lower Extremities in Rheumatoid Arthritis. (Lymphangio- und Lymphadenographie der unteren Extremität bei Polyarthritis progressiva.) MÁLEK, P., BELÁN, A., KRIEGEL, F., and KOLC, J. (1960). *Fortschr. Röntgenstr.*, **92**, 620. 17 figs, 5 refs.

Clinical and Serological Observations in Rheumatoid Arthritis. PORUSH, J. G., and MEISELAS, L. E. (1960). *Acta rheum. scand.*, **6**, 38. 17 refs.

Significance of the Sensitized Sheep Cell Test in Rheumatoid Arthritis. HINTON, N. A., BENIANS, M. E., and KELLY, H. G. (1960). *Canad. med. Ass. J.*, **83**, 13. 2 figs, 15 refs.

Haemagglutination Reaction with Human and Rabbit Gamma Globulin (Rose-Waaler Reaction). (Considerazioni sulla reazione di emoagglutinazione con gammaglobuline umane e di coniglio [Reazione di Waaler-Rose].) INVERNIZZI, F., MAZZEI, D., LUPORINI, G., and DEL GIACCO, G. S. (1960). *Reumatismo*, **12**, 19.

Comparative Study of Some Recent Serologic Tests for Rheumatoid Arthritis. MIKKELSEN, W. M., DUFF, I. F., GOODSON, L., COULTER, W. H., and HERTZ, C. (1960). *Ann. intern. Med.*, **52**, 1051. 1 fig., 15 refs.

Incidence and Significance of Sero-Positive Tests for the Rheumatoid Factor in Non-rheumatoid Diseases. BARTFELD, H. (1960). *Ann. intern. Med.*, **52**, 1059. 1 fig., 46 refs.

ACTH, Cortisone, and Other Steroids

Persistence of Intra-Articular Steroid: Experience with Prednisolone Trimethylacetate. WILL, G., and MURDOCH, W. R. (1960). *Brit. med. J.*, **1**, 94. 6 refs.

Experiments were carried out at Glasgow Royal Infirmary designed to determine the relative persistence of certain steroids in the joint cavity following intra-articular injection. Specimens of sinovial fluid were obtained from fifty joints (49 knees and one elbow) at intervals after the injection and were then examined chromatographically for the presence of steroid.

In the first experiment prednisolone trimethylacetate was injected into eight joints and hydrocortisone acetate into eight, the sixteen joints being aspirated completely after 24 hours and the fluid examined. Prednisolone was identified in the fluid from all eight joints into which this was injected, but hydrocortisone was not recovered from any of the joints injected with this steroid. In a further experiment prednisolone was injected into 12 joints, which were aspirated at longer intervals. Prednisolone was present in the fluid up to 6 days after injection of 50 mg. As an extension of this, sixteen further joints were injected and the fluid examined 7 days later; prednisolone was not usually present when the original dose was below 50 mg.

Finally, five joints were aspirated 10 or 14 days after injection of 60 to 100 mg. prednisolone. Of three joints aspirated 10 days after injection, two contained steroid; there was no steroid in the fluid from two joints aspirated after 14 days. The steroid was detected in an elbow joint after 14 days, although the dose had been only 25 mg.

The rapid disappearance of hydrocortisone from the joint cavity confirms the findings of previous workers. Prednisolone detected in joint fluid was usually the free alcohol, and it is presumably this form which exerts an anti-inflammatory local action, the relatively insoluble trimethylacetate acting merely as a local application.

B. E. W. Mace.

ACTH-producing Pituitary Tumors following Adrenalectomy for Cushing's Syndrome. NELSON, D. H., MEAKIN, J. W., and THORN, G. W. (1960). *Ann. intern. Med.*, **52**, 560. 3 figs, 8 refs.

Ten patients, previously adrenalectomized for Cushing's syndrome, who have subsequently developed evidence of a disturbance of the pituitary gland, have been studied. All of these patients were very deeply pigmented. In eight cases a tumour of the pituitary gland was demonstrable either by roentgenologic examination or by such evidence plus restricted visual fields. In two cases, markedly elevated levels of ACTH were found in association with deep pigmentation, but no tumour of the pituitary was demonstrable. In five of the ten patients it was possible to demonstrate a level of plasma-ACTH above that usually observed in Addisonian patients, or in other patients in whom a bilateral adrenalectomy has been carried out. All five patients who did not have raised levels of plasma-ACTH, but who were deeply pigmented and who did have evidence of pituitary tumours following adrenalectomy for Cushing's syndrome, had received irradiation to the pituitary gland before the first plasma was obtained for ACTH assay. The average time from adrenalectomy to the appearance of the pituitary tumour was 3 years (range 1-8 years) and, as noted above, pituitary histological examination in two cases was reported to show cells of a "chromophobe type".—[*From the authors' summary.*]

Urinary Sodium Retention after ACTH Stimulation: a Rapid, Simple Screening Test for Adrenal Cortical Insufficiency. BATCHELOR, T. M., and MOSHER, R. E. (1960). *Amer. J. med. Sci.*, **239**, 175. 2 figs, 18 refs.

The rapid screening test for adrenocortical insufficiency described in this paper from Providence Hospital, Detroit, depends on the changes in the concentration of sodium in the urine 4 hours after an injection of 25 units ACTH (corticotrophin), a reduction of 50 per cent. or more in this concentration being indicative of sodium retention and thus of a responsive adrenal cortex. Several illustrative cases are described. The authors conclude that although the test does not necessarily reflect the over-all integrity of the complex functions of the adrenal cortex it does measure changes in mineralocorticoid activity, probably of the 11-17-oxysteroids, and point out that it is mainly this mineralo-corticoid deficiency which produces the serious clinical problems of adrenal insufficiency. *A. Gordon Beckett.*

Clinical Research on the Use of Dexamethasone by Intra- and Peri-articular Injection. (Ricerche cliniche sul 16-alfa metil-9-alfa-fluoro prednisolone (Desametasone) usato per iniazioni locali intra- e periarticolari.) MARRAZZI, G. (1960). *Reumatismo*, **12**, 43. 21 refs.

Intra-Articular Injection of Soluble Dexamethasone. (Dexametasona soluble intraarticular.) JUÁREZ ORELLANA, L. B. (1960). *Arch. argent. Reum.*, **23**, 27.

Other General Subjects

Mode of Action of Acetylsalicylic Acid (Aspirin) in Man. (Zur Kenntnis der Wirkung der Acetylsalicylsäure (Aspirin) beim Menschen.) ABELIN, I., and BERLI, W. (1960). *Schweiz. med. Wschr.*, **90**, 87. 1 fig., 30 refs.

In this communication from the Institute of Medical Chemistry, University of Berne, the authors discuss the observed fact that the administration of 1 to 1·5 g. acetylsalicylic acid (aspirin) in man produces a marked increase in the urinary excretion of the hormonal catechol amines adrenaline and noradrenaline and of their precursors, such as hydroxytyramine (dopamine). The total amount of catechol excreted in the urine is also significantly increased. The maximum increase usually

occurs some 2 to 3 hours after taking the aspirin, the amount excreted then gradually returning to normal.

The authors suggest that the increased blood levels of adrenaline and noradrenaline stimulates the anterior lobe of the hypophysis in its secretion of the adrenal cortical hormone ACTH (corticotrophin), this in turn causing secretion by the adrenal glands of therapeutically valuable steroids, the suggested chain of reaction being: acetylsalicylic acid→adrenaline-noradrenaline→ACTH →cortisone. *L. A. Elson.*

Mechanism of Action of Rubefacients. FULTON, G. P., FARBER, E. M., and MORECI, A. P. (1959). *J. invest. Derm.*, **33**, 317. 6 figs, 17 refs.

The effects of rubefacients on the semi-transparent cheek pouch of the Syrian hamster were assessed directly at Stanford University School of Medicine, San Francisco, by micromanipulatory methods, transillumination, and motion-picture recording with 16-mm. colour film. Dial with urethane provided anaesthesia, while the materials tested included esters of nicotine acid (ethyl, methyl, n-hexyl, and tetrahydrofurfuryl) in concentrations of 0·1 to 100 per cent. in mammalian Ringer's solution, essential oils (mustard, wintergreen, clove, capsicum, turpentine, and camphor), and histamine. Occasionally vasoconstrictive agents—adrenaline, noradrenaline, electric current, or cold Ringer's solution—were used beforehand to induce a standard vessel size if the arterioles were found to be in maximum dilatation.

With all groups of materials a maximal and comparable degree of vasodilatation was achieved regardless of concentration, suggesting an all-or-none response. There was simultaneous vasodilatation beyond the site of contact of the stimulant, indicating that the vasodilatation produced by rubefacients is mediated by a conducting mechanism with nerve-like properties acting upon smooth muscle units to give the all-or-nothing response. The only differences noted between the various agents were in latent period and duration of response. In a few cases an unexplained vasoconstriction was obtained with the agents used. The participating vessels included the arterioles, the precapillary sphincters, and the large venules, all of which contain smooth muscle. Capillaries participated only by passive dilatation due to increased blood flow. Local anaesthesia was found to abolish the effects noted above. In 100 per cent. concentration, all the materials tried produced the classic signs of inflammation. The authors feel that the results suggest that rubefacients act through local perivascular transmission of the vasodilator impulse. *Allene Scott.*

Sicca Syndrome (Sjögren's Syndrome). DENKO, C. W., and BERGENSTAL, D. M. (1960). *A.M.A. Arch. intern. Med.*, **105**, 849. 3 figs, 16 refs.

Role of Brucellosis in the Pathogenesis of Chronic Rheumatoid Disease. (Rola zakażeń pałeczkami Brucella w zespole chorobotwórczym przewlekłych schorzeń gośćcowych.) PIENIĄŻEK, P., and LUTYŃSKI, R. (1960). *Pol. Tyg. lek.*, **15**, 906. 24 refs.

Clinical Comparison of Chlorzoxazone and Zoxazolamine: With Special Reference to Use of Muscle Relaxants in Rheumatic Disease. PEAK, W. P., and SMITH, R. T. (1960). *Penn. med. J.*, **63**, 833. 1 fig., 7 refs.

Evaluation of the Toluene-Sulfonic Acid Test. BENEDEK, T. G. (1960). *Arch. interamer. Rheum.*, **3**, 139. 13 refs.

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